

Triglycerides, coronary heart disease, and stroke. Fibrates and omega-3 fatty acids retain an important, separate role in the treatment of high triglyceride, low HDL cholesterol, and type 2 diabetes-metabolic syndromes.

4/1/09 Update.

Charles J. Glueck MD, Medical Director, Alliance cholesterol Center
Cincinnati OH. ABC Building, 3200 Burnet Avenue, Cincinnati OH, 45229
Email: glueckch@healthall.com; Phone 513-585-7800; Fax 513-585-7950

TAKE HOME MESSAGES

- High triglycerides, usually accompanied by low HDL cholesterol are an independent, treatable risk factor for heart attack and stroke. In post menopausal women, high triglycerides are a very major risk factor for cardiovascular disease, at least as important as LDL cholesterol.
- About 50% of patients referred to regional lipid treatment centers have high triglycerides –low HDL cholesterol as their major lipid problem, not high LDL cholesterol.
- Treatment of choice for high triglycerides–low HDL cholesterol are fibrates, and with triglycerides >500mg/dl, fish oil preparations high in omega 3 fatty acids (Lovaza).
- Statins are great drugs for lowering LDL cholesterol, but once triglyceride is > 500 mg/dl, statins are not effective as triglyceride-lowering agents.

DRUGS FOR LOWERING TRIGLYCERIDE, RAISING HDL CHOLESTEROL

Fibric Acids	Omega-3 fatty acids	Niacin
1. Gemfibrozil	Lovaza	Niaspan
2. Tricor-fenofibrate		
3. Antara-fenofibrate		
4. Triglide-fenofibrate		
5. Trilipix		

Trilipix was derived from the tricor molecule, and was specifically studied for safety with simvastatin, atorvastatin, and rosuvastatin. As expected from published data over the past 8 years, the safety profile of the fibric acid (trilipix)—statin combination was good, which will allow the FDA warning on concurrent fibric acid—statin combinations to be dropped. Since at least 40% of all hyperlipidemic patients require BOTH a fibric acid—statin combination, this new development, which will culminate in a soon to be approved trilipix-crestor tablet, has major clinical importance.

MAJOR PUBLISHED STUDIES

1. Helsinki Heart Study
2. VA HIT Trial
3. Bezafibrate infarction prevention study (BIP)
4. Fenofibrate intervention and Event Lowering in Diabetes Study (FIELD)

Does lowering triglyceride reduce CHD events?

Yes. The Helsinki Heart Trial, VA HIT, BIP, and most recently, FIELD study reveals that lowering triglycerides, increasing HDL cholesterol with fibric acids reduces CHD events by about 30%, when compared to placebo.

Helsinki:

Lopid 1.2 g vs placebo, 34% reduction in CVD events, 71% in diabetic subgroup. Primary prevention (no previous CVD events).

VA-HIT

1. Lopid 1.2 g vs placebo, 22% reduction in CVD events, 32% reduction in diabetic subgroup.

FIELD Study (Amer Heart Assn, Late Breaking Abstract 11/14/05)

1. 9795 type 2 diabetics, 7664 without CHD excluded if TG > 443 mg/dl
2. By design, only 37% had hyperlipidemia
3. Rx Fenofibrate 200 mg/day vs placebo

4. Total CVD events reduced ($p = .035$)
5. CHD events reduced 25%, total CVD events reduced 19% if no prior cardiovascular disease
6. Significant reduction in retinopathy and albuminuria.

Clinical trials

Flushing Assessment Tool (FAST(c)): Psychometric Properties of a New Measure Assessing Flushing Symptoms and Clinical Impact of Niacin Therapy¹

A common adverse effect of niacin therapy is flushing, manifested by cutaneous warmth, redness, itching and/or tingling. The Flushing ASsessment Tool (FAST(c)) was developed to assess flushing symptoms and their impact on patients receiving niacin therapy. This study evaluated the reliability, validity and responsiveness of the FAST(c). The minimal important difference (MID) of the FAST(c) was also examined. This was a prospective, randomized, double-blind, placebo-controlled, parallel-group 8-week study conducted to evaluate the psychometric characteristics of the FAST(c). The instrument is administered daily using an electronic patient diary. The study was conducted at 41 clinical sites in the US. 276 patients with dyslipidaemia were randomized to treatment and were at least 18 years of age, with fasting laboratory values of low-density lipoprotein cholesterol (LDL-C) <250 mg/dL and one of the following: high-density lipoprotein cholesterol (HDL-C) <40 mg/dL for males or <50 mg/dL for females; or triglycerides (TG) ≥ 150 and ≤ 400 mg/dL; or LDL-C ≥ 70 mg/dL for patients with a history of coronary heart disease (CHD) or CHD risk equivalents, or ≥ 100 mg/dL for subjects with two risk factors, or ≥ 160 mg/dL for subjects with 0-1 risk factors. Patients were randomized (1 : 1 : 1) to receive niacin extended-release (NER) 500mg/day in week 1, 1000 mg/day in week 2 and 2000 mg/day in weeks 3-6/aspirin (acetylsalicylic acid [ASA]), NER/ASA placebo, or NER placebo/ASA placebo. FAST(c) test-retest reliability in stable patients during the first 2 weeks was demonstrated for overall flushing severity using patient and physician overall treatment effect (OTE) ratings (intraclass correlation coefficients of >0.7 for mean overall and individual flushing severity scores). Over the 6-week treatment period, FAST(c) scores demonstrated significant correlations with individual symptoms, impact on daily activities and sleep, and dissatisfaction related to flushing ($p < 0.01$). Changes in FAST(c) scores were associated with treatment satisfaction ($p < 0.01$) and patient- and physician-rated OTE ($p < 0.01$). Using patient-rated OTE, the mean maximum flushing severity scores improved 1.85 points in responders and only 0.18 points in non-responders ($p < 0.001$); responders were defined by improved patient- or physician-rated OTE. Among patients with flushing, mean maximum overall flushing scores differed between patients who subsequently discontinued due to flushing (7.9 points) and those who did not discontinue (4.7 points; $p < 0.001$). The probable range in this study for a detectable change in flushing symptoms (MID) was 0.29-0.38 points for mean flushing severity and 0.66-0.86 points for maximum flushing severity. The FAST(c) exhibited test-retest reliability, good evidence of construct validity, and, overall, flushing severity was responsive to change over time. The FAST(c) is a reliable and valid instrument for assessing the impact of niacin-induced flushing in patients with dyslipidaemia.

[Rosuvastatin and fenofibrate in patients with diabetes and low high density lipoprotein cholesterol: comparison of changes of lipid levels and some markers of inflammation.]²

Purpose. To compare lipid lowering profile and effects on markers of inflammation of rosuvastatin and fenofibrate in patients with type 2 diabetes with low high density lipoprotein (HDL) cholesterol (CH). **Methods.** We enrolled into randomized open comparative study 30 pts (20 women) aged 62.5 ± 7.2 (47 - 74) years with type 2 diabetes and low HDLCH level (below 1.0 mmol/l for men and 1.2 mmol/l for women). All patients had arterial hypertension, 25 - coronary heart disease, 4 - peripheral arterial disease. Baseline BMI was > 25 kg/m² in all patients (above 30 kg/m² in 70%). Median waist circumference was 105.5 cm. Patients were assigned to receive either rosuvastatin 10 mg/day ($n=17$) or fenofibrate 200 mg/day ($n=13$). Serum lipids, high sensitivity C reactive protein (CPR), interleukin 6 (IL - 6) and fibrinogen levels were measured at baseline and after 3 months. **Results.** Median fasting glucose and HbA1c were 9.14 mmol/l and 6.8%, 8.78 mmol/l and 7.0% at baseline and study end respectively, without significant differences between groups. Mean baseline levels of low density lipoprotein (LDL) CH, HDLCH and triglycerides (TG) were 3.9, 0.93, and 2.39 mmol/l, respectively. Median baseline CRP was relatively low (1.5, interquartile range 0.78 - 3.08 mg/l). Both rosuvastatin and fenofibrate decreased total CH, LDLCH and TG and increased HDLCH. Tendencies to more pronounced effect of rosuvastatin on total and LDL CH and fenofibrate on TG and HDLCH were not statistically significant. CPR, IL - 6, and fibrinogen levels did not significantly change in either group. There were no associations between changes of lipid levels and those of CRP or IL - 6 when all patients were taken together. **Conclusion.** In this relatively small group of overweight diabetics with low HDLCH rosuvastatin and fenofibrate exerted expected effects on lipid profile. However 3 months administration of both starting dose of rosuvastatin (10 mg) and standard dose of fenofibrate was similarly neutral relative to CPR, IL - 6 and fibrinogen levels. This can reflect true absence of marked effect or be a consequence of low baseline values of these markers of inflammation.

The triglyceride/high-density lipoprotein cholesterol ratio predicts all-cause mortality in women with suspected

myocardial ischemia: a report from the Women's Ischemia Syndrome Evaluation (WISE) ³

High triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) are important cardiovascular risk factors in women. The prognostic utility of the TG/HDL-C ratio, a marker for insulin resistance and small dense low-density lipoprotein particles, is unknown among high-risk women. **METHODS:** We studied 544 women without prior myocardial infarction or coronary revascularization, referred for clinically indicated coronary angiography and enrolled in the Women's Ischemia Syndrome Evaluation (WISE). Fasting lipid profiles and detailed demographic and clinical data were obtained at baseline. Multivariate Cox-proportional hazards models for all-cause mortality and cardiovascular events (death, myocardial infarction, heart failure, stroke) over a median follow-up of 6 years were constructed using log TG/HDL-C ratio as a predictor variable and accounting for traditional cardiovascular risk factors. **RESULTS:** Mean age was 57 +/- 11 years; 84% were white, 55% hypertensive, 20% diabetic, 50% current or prior smokers. Triglyceride/HDL-C ranged from 0.3 to 18.4 (median 2.2, first quartile 0.35 to <1.4, fourth quartile 3.66-18.4). Deaths (n = 33) and cardiovascular events (n = 83) increased across TG/HDL-C quartiles (both P < .05 for trend). Triglyceride/HDL-C was a strong independent predictor of mortality in models adjusted for age, race, smoking, hypertension, diabetes, and angiographic coronary disease severity (hazard ratio 1.95, 95% CI 1.05-3.64, P = .04). For cardiovascular events, the multivariate hazard ratio was 1.54 (95% CI 1.05-2.22, P = .03) when adjusted for demographic and clinical variables, but became nonsignificant when angiographic results were included. **CONCLUSION:** Among women with suspected ischemia, the TG/HDL-C ratio is a powerful independent predictor of all-cause mortality and cardiovascular events.

Contemporary trends in dyslipidemia in the Framingham Heart Study ⁴

BACKGROUND: Recent cross-sectional population studies in the United States have shown an increase in obesity, a decrease in cholesterol values, but no changes in levels of high-density lipoprotein cholesterol (HDL-C) or triglycerides (TG). **METHODS:** Plasma total cholesterol, HDL-C, and TG levels, measured by the same methods at the 3 most recently completed examinations of Framingham Offspring Study participants (1991-2001), were compared in 1666 participants without prevalent cardiovascular disease, lipid therapy, or hormone replacement therapy (56% were men; mean ages of participants at the first and last examinations, 53 and 60 years, respectively). Changes in age- and multivariate-adjusted mean lipid levels were related to changes in body mass index (BMI). **RESULTS:** Over the 3 examinations, comparing the findings of the earliest examination with those of the most recent examination, the mean HDL-C level was significantly increased (multivariate-adjusted means, 44.4 and 46.6 mg/dL in men; 56.9 and 60.1 mg/dL in women; P value for trend, P < .001 in both sexes), whereas levels of TG were decreased (144.5 and 134.1 mg/dL in men; 122.3 and 112.3 mg/dL in women; P value for trend, P = .004 in men and < .001 in women). Over the same time interval, BMI (calculated as weight in kilograms divided by height in meters squared) increased (27.8 and 28.5 in men; 27.0 and 27.6 in women; P value for trend, P < .001 in men and P = .001 in women). There was an inverse relationship between changes in BMI and magnitude of dyslipidemia (ie, individuals with the least increase in BMI had the most favorable changes in levels of HDL-C and TG). **CONCLUSION:** During a 10-year period of recent examinations in the Framingham Heart Study there was a decrease in dyslipidemia with an increase in HDL-C levels and a decrease in levels of TG despite an overall increase in BMI.

Managing diabetic dyslipidemia: beyond statin therapy ⁵

Cardiovascular disease is a significant cause of morbidity and mortality in patients with diabetes mellitus. The lipid profile of type 2 diabetes mellitus is characterized by increased triglycerides (TGs), decreased high-density lipoprotein cholesterol (HDL-C), increased very low density lipoproteins (VLDLs), and small, dense low-density lipoprotein particles, the combination of which is highly atherogenic. In diabetic patients, current treatment guidelines target low-density lipoprotein cholesterol (LDL-C) <or= 100 mg/dL with statins. In patients with elevated TGs, non-HDL-C is considered a secondary target of therapy. Despite the use of statin therapy in diabetes, a significant number of fatal and nonfatal coronary heart disease (CHD) events still occur, indicating the need to target other modifiable risk factors for CHD, including high TGs and low HDL-C.

Effects of extended-release niacin on lipid profile and adipocyte biology in patients with impaired glucose tolerance

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BACKGROUND: Low high-density lipoprotein cholesterol (HDL-C) serum concentrations are independent risk factors for the development of coronary artery disease. In patients with the metabolic syndrome, low HDL-C can contribute to premature atherosclerosis. Extended-release (ER) niacin increases HDL-C and was shown to slow the progression of atherosclerosis. Adipose tissue is an important site of niacin action. Here we sought to determine potential pleiotropic effects of ER niacin on adipose tissue biology in patients with impaired glucose tolerance (IGT). **METHODS AND RESULTS:** Thirty patients with IGT (mean age=45.2+/-3.9 years), low HDL-C serum concentrations (HDL-C <1.0mmol/l), but no additional comorbidities were treated once-daily with ER niacin (1000mg) in a randomized open-label controlled (n=30) study for 6 months. During the first 4 weeks, daily dose was increased from 375 to 1000mg in weekly intervals. At baseline and after 6 months, subcutaneous adipose tissue biopsies were taken, body fat mass, insulin sensitivity (euglycemic-hyperinsulinemic clamp),

and adipokine serum concentrations were measured. After 6 months of ER niacin treatment, HDL-C increased significantly by 24% and adiponectin by 35%. In addition, ER niacin significantly reduced circulating lipoprotein (a) by 38% ($p < 0.001$) and fasting triglycerides by 12% ($p < 0.05$). Whole-body insulin sensitivity increased in the ER niacin treatment group, although this trend was not statistically significant ($p = 0.085$). Six months ER niacin led to a significant reduction in mean adipocyte size associated with increased insulin sensitivity in isolated adipocytes and gene expression changes including increased adiponectin, C/EBP α , C/EBP δ , PPAR γ and decreased carnitine palmitoyl transferase 2, hormone sensitive lipase, nicotinic acid receptor (GPR109B) and fatty-acid synthase mRNA expression. **CONCLUSION:** Treatment with ER niacin significantly improves atherogenic lipid profile in patients with IGT. These beneficial effects could at least in part be due to pleiotropic niacin effects in adipose tissue, characterized by decreased mean adipocyte size, increased insulin sensitivity and altered mRNA expression profile.

Effect of rimonabant on the high-triglyceride/ low-HDL-cholesterol dyslipidemia, intraabdominal adiposity, and liver fat: the ADAGIO-Lipids trial⁷.

BACKGROUND: Rimonabant, the first selective cannabinoid type 1 (CB1) receptor antagonist, improves cardiometabolic risk factors in overweight/obese patients. ADAGIO-Lipids assessed the effect of rimonabant on cardiometabolic risk factors and intraabdominal and liver fat. **METHODS AND RESULTS:** 803 abdominally obese patients with atherogenic dyslipidemia (increased triglycerides [TG] or reduced high-density lipoprotein-cholesterol [HDL-C]) were randomized to placebo or rimonabant 20 mg/d for 1 year. HDL-C and TG were coprimary end points. Intraabdominal (visceral) and liver fat were measured by computed tomography in a subgroup of 231 patients. In total, 73% of rimonabant- and 70% of placebo-treated patients completed the study treatment. Rimonabant 20 mg produced significantly greater changes from baseline versus placebo in HDL-C (+7.4%) and TG levels (-18%; $P < 0.0001$), as well as low-density lipoprotein (LDL) and HDL particle sizes, apolipoprotein A1 and B, HDL2, HDL3, C-reactive protein, and adiponectin levels (all $P < 0.05$). Rimonabant decreased abdominal subcutaneous adipose tissue (AT) cross-sectional area by 5.1% compared to placebo ($P < 0.005$), with a greater reduction in visceral AT (-10.1% compared to placebo; $P < 0.0005$), thereby reducing the ratio of visceral/subcutaneous AT ($P < 0.05$). Rimonabant significantly reduced liver fat content (liver/spleen attenuation ratio; $P < 0.005$). Systolic (-3.3 mm Hg) and diastolic (-2.4 mm Hg) blood pressure were significantly reduced with rimonabant versus placebo ($P < 0.0001$). The safety profile of rimonabant was consistent with previous studies; gastrointestinal, nervous system, psychiatric, and general adverse events were more common with rimonabant 20 mg. **CONCLUSIONS:** In abdominally obese patients with atherogenic dyslipidemia, rimonabant 20 mg significantly improved multiple cardiometabolic risk markers and induced significant reductions in both intraabdominal and liver fat.

Effect of a Combined Therapeutic Approach of Intensive Lipid Management, Omega-3 Fatty Acid Supplementation, and Increased Serum 25 (OH) Vitamin D on Coronary Calcium Scores in Asymptomatic Adults⁸.

The impact of intensive lipid management, omega-3 fatty acid, and vitamin D3 supplementation on atherosclerotic plaque was assessed through serial computed tomography coronary calcium scoring (CCS). Low-density lipoprotein cholesterol reduction with statin therapy has not been shown to reduce or slow progression of serial CCS in several recent studies, casting doubt on the usefulness of this approach for tracking atherosclerotic progression. In an open-label study, 45 male and female subjects with CCS of ≥ 50 without symptoms of heart disease were treated with statin therapy, niacin, and omega-3 fatty acid supplementation to achieve low-density lipoprotein cholesterol and triglycerides ≤ 60 mg/dL; high-density lipoprotein ≥ 60 mg/dL; and vitamin D3 supplementation to achieve serum levels of ≥ 50 ng/mL 25(OH) vitamin D, in addition to diet advice. Lipid profiles of subjects were significantly changed as follows: total cholesterol -24%, low-density lipoprotein -41%; triglycerides -42%, high-density lipoprotein +19%, and mean serum 25(OH) vitamin D levels +83%. After a mean of 18 months, 20 subjects experienced decrease in CCS with mean change of -14.5% (range 0% to -64%); 22 subjects experienced no change or slow annual rate of CCS increase of +12% (range 1%-29%). Only 3 subjects experienced annual CCS progression exceeding 29% (44%-71%). Despite wide variation in response, substantial reduction of CCS was achieved in 44% of subjects and slowed plaque growth in 49% of the subjects applying a broad treatment program.

Perturbation of phospholipid and triacylglycerol fatty acid positional location in the heart of rats depleted of n-3 long-chain polyunsaturates⁹.

Rats depleted of long-chain polyunsaturated n-3 fatty acids (n-3-D) display several features of the metabolic syndrome, including obesity, liver steatosis, insulin resistance, hypertension, and cardiac hypertrophy. In this study, the heart phospholipid (PL) and triacylglycerol (TG) fatty acid content and pattern were compared between female control rats (C) and n-3-D rats. The sole n-3 fatty acids found in n-3-D rats, C22:5(n-3) and C22:6(n-3), were 10 to 20 times lower than in C. The total fatty acid content of PL was lower in n-3-D rats than C. No ectopic TG accumulation was found in n-3-D rats. In both PL and TG, the C16:0/C16:1(n-7) and C18:0/C18:1(n-9) ratios suggested increased Delta9-desaturase activity in n-3-D rats. The PL C18:2(n-6)/C20:4(n-6) and C20:4(n-6)/C22:4(n-6) ratios were also lower in n-3-D rats than C. Prior intravenous injection of a medium-chain TG:fish oil emulsion to n-3-D rats 60 to 120 minutes before killing augmented the PL content in

C22:5(n-3) and C22:6(n-3), minimized the age-related decrease in the PL C18:1(n-9) relative content, and increased the TG C22:4(n-6) content. The alteration of cardiac function in n-3-D rats and its improvement after injection of medium-chain TG:fish oil emulsion coincides with parallel changes in heart lipid fatty acid content and pattern.

Lipids, lipid modifying agents and cardiovascular risk: a review of the evidence¹⁰

Abstract It is well established that serum total-cholesterol, LDL-cholesterol, low HDL-cholesterol and calculated indices such as total cholesterol to HDL-cholesterol ratio or less commonly used indices such as non-HDL cholesterol are strongly predictive of cardiovascular events. Serum triglycerides, by contrast, are only modestly associated with coronary heart disease (CHD) in multivariate analysis and incorporation of triglycerides into prediction algorithms is therefore unlikely to improve their prediction capability. Meta-analysis of studies including >90 000 subjects has provided robust evidence that statins reduce important clinical endpoints. These included a 12% fall in all-cause mortality, 19% fall in CHD mortality and 23% fall in CHD mortality or myocardial infarction. Furthermore there are high quality data showing additional benefit of intensive statin therapy over standard statin therapy for secondary prevention of cardiovascular disease. However, meta-analysis of 10 fibrate trials has shown inconsistent evidence of vascular benefit and non-cardiovascular mortality has been slightly but consistently elevated in most fibrate trials and in meta-analysis. The general use of fibrates for cardiovascular risk reduction can therefore not be supported at present. Other second line agents such as bile acid sequestrants, nicotinic acid and omega-3 fatty acid supplements have been evaluated in a few randomised controlled studies in which cardiovascular benefit has been found but clearly further data are required to properly establish their use in clinical practice. Ongoing studies such as ACCORD, IMPROVE-IT, ASCEND, ORIGIN and HPS2-THRIVE should assist in answering outstanding questions over the next 5 years.

Fixed-dose combination of extended-release niacin plus simvastatin for lipid disorders¹¹

Coronary heart disease (CHD) carries significant morbidity and mortality worldwide. Elevated LDL-cholesterol and reduced HDL-cholesterol levels are well-recognized CHD risk factors. Despite guideline recommendations for intensive therapy among patients at high risk for CHD to lower LDL-cholesterol, such lowering has failed to prevent approximately two-thirds of cardiovascular events. As a result of new data, guidelines have begun to focus on non-HDL-cholesterol, HDL-cholesterol and triglycerides as treatment targets, with the end result being a recommendation for combination therapy, such as niacin plus statin for the treatment of dyslipidemia. Compared with statin monotherapy, a combination of niacin and statin therapy provides beneficial effects on a broad range of lipid particles and some evidence suggests a further reduction in CHD risk. Recent studies have shown that the combination of a fixed dose of extended-release niacin plus simvastatin reduces non-HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol:HDL-cholesterol ratio by approximately 50% while increasing HDL-cholesterol by 25%. The safety of this combination is consistent with the safety profiles of each individual component and is well tolerated. A long-term study is currently being conducted to evaluate whether this combination therapy confers an additive impact on clinical end points.

Pathologic findings in rabbit models of hereditary hypertriglyceridemia and hereditary postprandial hypertriglyceridemia¹²

In recent years, the association between hyperlipidemia and the development of arteriosclerosis has been addressed in several studies. Rabbit models of hypertriglyceridemia (TGH) and postprandial hypertriglyceridemia (PHT) have been developed at the authors' institute. TGH rabbits manifest pathology similar to that of humans with TGH, such as xanthoma, in addition to atherosclerosis of arterioles. Furthermore, PHT rabbits show visceral obesity, insulin resistance, and impaired glucose tolerance, with pathologic features similar to those of the metabolic syndrome assumed to be the cause of human ischemic heart disease. This study was designed to investigate the histopathologic features of TGH and PHT rabbits. TGH rabbits showed advanced aortic atherosclerosis, accompanied by intimal thickening of coronary and renal arteries, fatty liver changes, and xanthoma. PHT rabbits demonstrated aortic intimal thickening and hepatic fatty degeneration. The results of this study suggest that TGH and PHT rabbits are useful animal models for studying human hyperlipidemia and metabolic syndrome and the cardiovascular diseases that result from these conditions.

Nonfasting triglycerides and risk of ischemic stroke in the general population¹³

CONTEXT: The role of triglycerides in the risk of ischemic stroke remains controversial. Recently, a strong association was found between elevated levels of nonfasting triglycerides, which indicate the presence of remnant lipoproteins, and increased risk of ischemic heart disease. OBJECTIVE: To test the hypothesis that increased levels of nonfasting triglycerides are associated with ischemic stroke in the general population. DESIGN, SETTING, AND PARTICIPANTS: The Copenhagen City Heart Study, a prospective, Danish population-based cohort study initiated in 1976, with follow-up through July 2007. Participants were 13,956 men and women aged 20 through 93 years. A cross-sectional study included 9637 individuals attending the 1991-1994 examination of the prospective study. MAIN OUTCOME MEASURES: Prospective study: baseline levels of nonfasting triglycerides, other risk factors at baseline and at follow-up examinations, and incidence

of ischemic stroke. Cross-sectional study: levels of nonfasting triglycerides, levels of remnant cholesterol, and prevalence of ischemic stroke. RESULTS: Of the 13,956 participants in the prospective study, 1529 developed ischemic stroke. Cumulative incidence of ischemic stroke increased with increasing levels of nonfasting triglycerides (log-rank trend, $P < .001$). Men with elevated nonfasting triglyceride levels of 89 through 176 mg/dL had multivariate-adjusted hazard ratios (HRs) for ischemic stroke of 1.3 (95% CI, 0.8-1.9; 351 events); for 177 through 265 mg/dL, 1.6 (95% CI, 1.0-2.5; 189 events); for 266 through 353 mg/dL, 1.5 (95% CI, 0.9-2.7; 73 events); for 354 through 442 mg/dL, 2.2 (95% CI, 1.1-4.2; 40 events); and for 443 mg/dL or greater, 2.5 (95% CI, 1.3-4.8; 41 events) vs men with nonfasting levels less than 89 mg/dL (HR, 1.0; 85 events) ($P < .001$ for trend). Corresponding values for women were 1.3 (95% CI, 0.9-1.7; 407 events), 2.0 (95% CI, 1.3-2.9; 135 events), 1.4 (95% CI, 0.7-2.9; 26 events), 2.5 (95% CI, 1.0-6.4; 13 events), and 3.8 (95% CI, 1.3-11; 10 events) vs women with nonfasting triglyceride levels less than 89 mg/dL (HR, 1.0; 159 events) ($P < .001$ for trend). Absolute 10-year risk of ischemic stroke ranged from 2.6% in men younger than 55 years with nonfasting triglyceride levels of less than 89 mg/dL to 16.7% in men aged 55 years or older with levels of 443 mg/dL or greater. Corresponding values in women were 1.9% and 12.2%. In the cross-sectional study, men with a previous ischemic stroke vs controls had nonfasting triglyceride levels of 191 (IQR, 131-259) mg/dL vs 148 (IQR, 104-214) mg/dL ($P < .01$); corresponding values for women were 167 (IQR, 121-229) mg/dL vs 127 (IQR, 91-181) mg/dL ($P < .05$). For remnant cholesterol, corresponding values were 38 (IQR, 26-51) mg/dL vs 29 (IQR, 20-42) mg/dL in men ($P < .01$) and 33 (IQR, 24-45) mg/dL vs 25 (IQR, 18-35) mg/dL in women ($P < .05$). CONCLUSION: In this study population, nonfasting triglyceride levels were associated with risk of ischemic stroke.

Baseline blood pressure, low- and high-density lipoproteins, and triglycerides and the risk of vascular events in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial¹⁴

OBJECTIVE: To explore the relative contributions of baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) and lipoproteins on the risk of recurrent stroke or first major cardiovascular event (MCVE) and their potential impact on the benefit of statin treatment. METHODS AND RESULTS: The SPARCL trial randomized 4731 patients with recent stroke or transient ischemic attack (TIA) and no known coronary heart disease and LDL-C between 100 and 190mg/dL to either atorvastatin 80mg/d or placebo. Baseline assessment included SBP, DBP and measurements of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and triglyceride levels. After 4.9 years of follow-up, there were 575 primary end points (fatal and nonfatal stroke), including 491 ischemic strokes, and 740 MCVEs (stroke plus myocardial infarction and vascular death). Cox regression models analysis showed a trend ($P > 0.05$ and $P < 0.10$) for higher SBP but not DBP to be associated with an outcome stroke with only SBP associated with MCVE. Only baseline low HDL-C was associated with an outcome stroke. Baseline HDL-C, triglycerides, and LDL/HDL ratio were each associated with MCVEs. There were no interactions between any of these baseline variables and the effect of treatment on outcome strokes. CONCLUSIONS: In patients with recent stroke or TIA and no coronary heart disease, only lower baseline HDL-C predicted the risk of recurrent stroke with HDL-C, triglycerides, and LDL/HDL ratio associated with MCVE. Atorvastatin treatment was similarly effective regardless of baseline lipoprotein levels.

The role of triglycerides in cardiovascular risk¹⁵

Triglycerides' role in coronary heart disease (CHD) risk assessment has long been debated. Although meta-analyses have suggested that triglycerides are an independent risk factor for CHD, a consensus has emerged that triglycerides more appropriately represent a biomarker of CHD risk rather than an independent risk factor. Ongoing studies will determine whether triglyceride lowering confers additional CHD benefit beyond that attained via low-density lipoprotein (LDL) cholesterol reduction. The American Diabetes Association presently recommends lowering elevated triglycerides as a secondary therapeutic target after LDL cholesterol, whereas other organizations, such as the National Cholesterol Education Program, recommend non-high-density lipoprotein cholesterol as the second priority after attaining the LDL cholesterol goal. However, reducing very high triglycerides (ie, > 500 mg/dL) remains a sufficiently high priority in affected individuals.

Secular trends in cholesterol lipoproteins and triglycerides and prevalence of dyslipidemias in an urban Indian population¹⁶

BACKGROUND: Coronary heart disease is increasing in urban Indian subjects and lipid abnormalities are important risk factors. To determine secular trends in prevalence of various lipid abnormalities we performed studies in an urban Indian population. METHODS: Successive epidemiological Jaipur Heart Watch (JHW) studies were performed in Western India in urban locations. The studies evaluated adults $>$ or $= 20$ years for multiple coronary risk factors using standardized methodology (JHW-1, 1993-94, $n = 2212$; JHW-2, 1999-2001, $n = 1123$; JHW-3, 2002-03, $n = 458$, and JHW-4 2004-2005, $n = 1127$). For the present analyses data of subjects 20-59 years ($n = 4136$, men 2341, women 1795) have been included. In successive studies, fasting measurements for cholesterol lipoproteins (total cholesterol, LDL cholesterol, HDL cholesterol) and triglycerides were performed in 193, 454, 179 and 252 men ($n = 1078$) and 83, 472, 195, 248 women ($n = 998$) respectively (total 2076). Age-group specific levels of various cholesterol lipoproteins, triglycerides and their ratios were

determined. Prevalence of various dyslipidemias (total cholesterol \geq 200 mg/dl, LDL cholesterol \geq 130 mg/dl, non-HDL cholesterol \geq 160 mg/dl, triglycerides \geq 150 mg/dl, low HDL cholesterol $<$ 40 mg/dl, high cholesterol remnants \geq 25 mg/dl, and high total:HDL cholesterol ratio \geq 5.0, and \geq 4.0) were also determined. Significance of secular trends in prevalence of dyslipidemias was determined using linear-curve estimation regression. Association of changing trends in prevalence of dyslipidemias with trends in educational status, obesity and truncal obesity (high waist:hip ratio) were determined using two-line regression analysis. RESULTS: Mean levels of various lipoproteins increased sharply from JHW-1 to JHW-2 and then gradually in JHW-3 and JHW-4. Age-adjusted mean values (mg/dl) in JHW-1, JHW-2, JHW-3 and JHW-4 studies respectively showed a significant increase in total cholesterol (174.9 \pm 45, 196.0 \pm 42, 187.5 \pm 38, 193.5 \pm 39, 2-stage least-squares regression $R = 0.11$, $p < 0.001$), LDL cholesterol (106.2 \pm 40, 127.6 \pm 39, 122.6 \pm 44, 119.2 \pm 31, $R = 0.11$, $p < 0.001$), non-HDL cholesterol (131.3 \pm 43, 156.4 \pm 43, 150.1 \pm 41, 150.9 \pm 32, $R = 0.12$, $p < 0.001$), remnant cholesterol (25.1 \pm 11, 28.9 \pm 14, 26.0 \pm 11, 31.7 \pm 14, $R = 0.06$, $p = 0.001$), total:HDL cholesterol ratio (4.26 \pm 1.3, 5.18 \pm 1.7, 5.21 \pm 1.7, 4.69 \pm 1.2, $R = 0.10$, $p < 0.001$) and triglycerides (125.6 \pm 53, 144.5 \pm 71, 130.1 \pm 57, 158.7 \pm 72, $R = 0.06$, $p = 0.001$) and decrease in HDL cholesterol (43.6 \pm 14, 39.7 \pm 8, 37.3 \pm 6, 42.5 \pm 6, $R = 0.04$, $p = 0.027$). Trends in age-adjusted prevalence (%) of dyslipidemias in JHW-1, JHW-2, JHW-3 and JHW-4 studies respectively showed insignificant changes in high total cholesterol (26.3, 35.1, 25.6, 26.0, linear curve-estimation coefficient multiple $R = 0.034$), high LDL cholesterol \geq 130 mg/dl (24.2, 36.2, 31.0, 22.2, $R = 0.062$), and high low HDL cholesterol $<$ 40 mg/dl (46.2, 53.3, 55.4, 33.7, $R = 0.136$). Increase was observed in prevalence of high non-HDL cholesterol (23.0, 33.5, 27.4, 26.6, $R = 0.026$), high remnant cholesterol (40.1, 40.3, 30.1, 60.6, $R = 0.143$), high total:HDL cholesterol ratio \geq 5.0 (22.2, 47.6, 53.2, 26.3, $R = 0.031$) and \geq 4.0 (58.6, 72.5, 70.1, 62.0, $R = 0.006$), and high triglycerides (25.7, 28.2, 17.5, 34.2, $R = 0.047$). Greater correlation of increasing non-HDL cholesterol, remnant cholesterol, triglycerides and total:HDL cholesterol ratio was observed with increasing truncal obesity than generalized obesity (two-line regression analysis $p < 0.05$). Greater educational level, as marker of socioeconomic status, correlated significantly with increasing obesity (r^2 men 0.98, women 0.99), and truncal obesity (r^2 men 0.71, women 0.90). CONCLUSION: In an urban Indian population, trends reveal increase in mean total-, non-HDL-, remnant-, and total:HDL cholesterol, and triglycerides and decline in HDL cholesterol levels. Prevalence of subjects with high total cholesterol did not change significantly while those with high non-HDL cholesterol, cholesterol remnants, triglycerides and total-HDL cholesterol ratio increased. Increasing dyslipidemias correlate significantly with increasing truncal obesity and obesity.

Effect of rimonabant, micronised fenofibrate and their combination on cardiometabolic risk factors in overweight/obese patients: a pilot study¹⁷.

OBJECTIVE: To assess the effect of rimonabant, micronised fenofibrate and their combination on anthropometric and metabolic parameters in overweight/obese patients with dyslipidaemia. METHODS: All patients ($n = 30$) received a hypocaloric diet (approximately 600 kcal/day deficit) and were randomly allocated to receive open-label rimonabant (R) 20 mg/day ($n = 10$), micronised fenofibrate (F) 200 mg/day ($n = 10$) or rimonabant 20 mg/day plus fenofibrate 200 mg/day (RF) ($n = 10$). Anthropometric and metabolic parameters were assessed at baseline and 3 months after treatment initiation. RESULTS: Compared with baseline similar significant reductions in body weight, body mass index and waist circumference were observed in the R (-6, -5 and -5%, respectively; $p < 0.01$) and RF group (-5% for all, $p < 0.05$), while improvements in these parameters were smaller in the F group (-2, -2.5 and -2%, respectively; $p < 0.05$). Triglycerides were reduced by 18% in the R group ($p = \text{NS}$), by 39% in the F group ($p < 0.001$) and by 46% in the RF group ($p < 0.05$). Importantly, combination treatment resulted in a 42% increase in high-density lipoprotein cholesterol (HDL-C) levels ($p < 0.05$), while HDL-C was not significantly altered in the two monotherapy groups. Subsequently, a more pronounced increase in apolipoprotein A-I (ApoA-I) levels (+25%) was observed in the RF group compared with changes in both monotherapy groups ($p < 0.0001$ vs R and $p < 0.005$ vs F group). Low-density lipoprotein cholesterol (LDL-C) levels were not significantly altered in any group. Apolipoprotein B (apoB) levels were reduced in all groups and this reduction was significantly more pronounced in the RF group ($p < 0.05$ vs baseline as well as $p < 0.005$ and $p < 0.01$ for RF vs R and F groups, respectively). ApoB/apoA-I ratio decreased by 3% with R ($p = \text{NS}$), by 18% with F ($p < 0.05$) and by 40% with RF treatment ($p < 0.01$). Total cholesterol to HDL-C ratio decreased by 20% with F ($p < 0.0001$) and by 33% with RF therapy ($p < 0.005$), while it was not significantly altered in R group. CONCLUSION: The combination of rimonabant and fenofibrate may further improve metabolic parameters in overweight/obese patients with dyslipidaemia compared with each monotherapy. This improvement is particularly pronounced for HDL-C levels.

Genome-wide linkage scan for genes influencing plasma triglyceride levels in the Veterans Administration Genetic Epidemiology Study¹⁸.

OBJECTIVE: Elevated plasma triglyceride concentration is a component of the insulin resistance syndrome and is commonly associated with type 2 diabetes, obesity, and coronary heart disease. The goal of our study was to perform a genome-wide linkage scan to identify genetic regions that influence variation in plasma triglyceride levels in families that are enriched with individuals with type 2 diabetes. RESEARCH DESIGN AND METHODS: We used phenotypic and genotypic data from 1,026 individuals distributed across 294 Mexican-American families, who were ascertained for type 2 diabetes, from the Veterans Administration Genetic Epidemiology Study (VAGES). Plasma triglyceride values were transformed, and

a variance-components technique was used to conduct multipoint linkage analysis. RESULTS: After adjusting for the significant effects of sex and BMI, heritability for plasma triglycerides was estimated as 46 +/- 7% ($P < 0.0001$). Multipoint linkage analysis yielded the strongest evidence for linkage of plasma triglycerides near marker D12S391 on chromosome 12p (logarithm of odds [LOD] = 2.4). Our linkage signal on chromosome 12p provides independent replication of a similar finding in another Mexican-American sample from the San Antonio Family Diabetes Study (SAFDS). Combined multipoint linkage analysis of the VAGES and SAFDS data yielded significant evidence for linkage of plasma triglycerides to a genetic location between markers GATA49D12 and D12S391 on 12p (LOD = 3.8, empirical P value = 2.0×10^{-5}). This region on 12p harbors the gene-encoding adiponectin receptor 2 (AdipoR2), where we previously have shown that multiple single nucleotide polymorphisms are associated with plasma triglyceride concentrations in the SAFDS. In the present study, we provided suggestive evidence in favor of association for rs929434 with triglyceride concentrations in the VAGES. CONCLUSIONS: Collectively, these results provide strong evidence for a major locus on chromosome 12p that influences plasma triglyceride levels in Mexican Americans.

Effectiveness of combined statin plus omega-3 fatty acid therapy for mixed dyslipidemia¹⁹

Combination therapy for the treatment of dyslipidemia and reduction of cardiovascular risk has been demonstrated to beneficially modify the lipid profile in multiple randomized clinical trials. As reported in the updated National Cholesterol Education Program Adult Treatment Panel III guidelines, low-density lipoprotein (LDL) cholesterol remains the primary treatment target, although the comprehensive management of dyslipidemia in high-risk patients includes the modification of secondary lipid parameters such as triglycerides, high-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol. Although statin therapy is the standard intervention for lowering LDL cholesterol, combination therapy has demonstrated added benefits on secondary lipid parameters and enhances statin-mediated reductions in LDL cholesterol. The benefits of modifying these secondary targets on all-cause or cardiovascular event-related mortality are currently under investigation in several clinical trials. Prescription omega-3 fatty acid (Lovaza) is a formulation of 2 highly purified omega-3-acid ethyl esters, eicosapentaenoic acid and docosahexaenoic acid. The recently completed Combination of Prescription Omega-3 With Simvastatin (COMBOS) study confirmed that prescription omega-3 fatty acid administered in combination with simvastatin achieves statistically significant improvements across a range of lipid indicators beyond the LDL primary target, including triglycerides, non-high-density lipoprotein cholesterol, and lipoprotein particle size. In conclusion, several classes of drugs, including omega-3 fatty acids, can be used in combination with statins to achieve more global improvements in lipid profiles.

Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function²⁰

OBJECTIVES: This study sought to assess the effects of prolonged caloric restriction in obese patients with type 2 diabetes mellitus (T2DM) on myocardial triglyceride (TG) content and myocardial function. BACKGROUND: Myocardial TG content is increased in patients with T2DM and may reflect altered myocardial function. It is unknown whether myocardial TG content is influenced during a therapeutic intervention. METHODS: Myocardial TG content (magnetic resonance [MR] spectroscopy), myocardial function (MR imaging), plasma hemoglobin A1c, and body mass index (BMI) were measured in 12 obese, insulin-treated T2DM patients before and after a 16-week very-low-calorie diet (VLCD) (450 kcal/day) to achieve substantial weight loss. Insulin was stopped during the VLCD. RESULTS: The BMI decreased from 35.6 +/- 1.2 kg/m² (baseline, mean +/- SEM) to 27.5 +/- 1.3 kg/m² (after the VLCD, $p < 0.001$) and was associated with an improvement in hemoglobin A1c from 7.9 +/- 0.4% (baseline) to 6.3 +/- 0.3% (after the VLCD, $p = 0.006$). Myocardial TG content decreased from 0.88 +/- 0.12% to 0.64 +/- 0.14%, respectively ($p = 0.019$), and was associated with improved diastolic function (reflected by the ratio between the early and atrial filling phase) from 1.02 +/- 0.08 to 1.18 +/- 0.06, respectively ($p = 0.019$). CONCLUSIONS: Prolonged caloric restriction in obese T2DM patients decreases BMI and improves glucoregulation associated with decreased myocardial TG content and improved diastolic heart function. Therefore, myocardial TG stores in obese patients with T2DM are flexible and amendable to therapeutic intervention by caloric restriction.

Evaluation of a new formulation of fenofibric acid, ABT-335, co-administered with statins : study design and rationale of a phase III clinical programme²¹

BACKGROUND and objective: Atherogenic lipid parameters in patients with mixed dyslipidaemia have been demonstrated to increase atherosclerotic coronary heart disease (CHD) risk. Clinical studies have shown that HMG-CoA reductase inhibitor (statin) and fibric acid derivative (fibrate) combination therapy is effective at improving multiple lipid abnormalities in different patient populations at increased risk of CHD. However, inconsistencies with respect to trial designs and safety issues have limited the clinical use of this combination therapy. A comprehensive, controlled clinical trial programme was thus designed to evaluate three separate statins in combination with ABT-335, a new formulation of fenofibric acid. METHODS: Three separate 22-week, phase III, double-blind, active-controlled trials will evaluate combination therapy with ABT-335 135 mg/day and either rosuvastatin (10 mg/day and 20 mg/day), atorvastatin (20 mg/day and 40 mg/day) or simvastatin (20 mg/day and 40 mg/day) in comparison to either ABT-335 or the corresponding statin monotherapy. An

approximate total of 2400 patients with elevated triglycerides (TG) [\geq or =150 mg/dL], reduced high-density lipoprotein cholesterol (HDL-C) [$<$ 40 mg/dL for men and $<$ 50 mg/dL for women], and elevated low-density lipoprotein cholesterol (LDL-C) [\geq or =130 mg/dL] will be randomized to one of six intervention arms per trial (two combination therapy and four monotherapy groups). The pre-specified primary efficacy endpoint is a composite of the mean percent changes in HDL-C and TG (comparing each combination therapy with the corresponding statin monotherapy dose) and LDL-C (comparing each combination therapy with ABT-335 monotherapy). Secondary endpoints include mean percent changes in non-HDL-C, very LDL-C, total cholesterol, apolipoprotein B and high sensitivity C-reactive protein levels. At study end, patients may enroll in a 12-month open-label extension study that will evaluate the long-term efficacy and safety of combination therapy. CONCLUSION: This is the largest phase III randomized, controlled clinical programme to date evaluating the efficacy and safety of the combined use of a new formulation of fenofibric acid (ABT-335) with three commonly prescribed statins in patients with mixed dyslipidaemia.

Cold acclimation induces physiological cardiac hypertrophy and increases assimilation of triacylglycerol metabolism through lipoprotein lipase²²

The contribution of triacylglycerol to energy provision in the hypertrophied heart, mediated through lipoprotein lipase (LPL) is largely unknown and the contribution of very-low-density lipoprotein (VLDL) receptor to control of LPL presentation at the endothelium is unclear. For isolated perfused rat hearts, cold acclimation (CA) induced volume-overload hypertrophy, with decreased developed pressure ($P<0.01$), increased end-diastolic volume of the left ventricle ($P<0.001$) and a loss of contractile reserve in response to dobutamine challenge ($P<0.01$). Oleate utilisation by perfused hearts was unchanged by CA, however uptake of intralipid emulsion increased 3-fold ($P<0.01$). CA increased the proportion of lipid deposited in tissue lipids from 10% in euthermic controls to 40% ($P<0.01$) although the overall contribution of individual lipid classes was unaffected. Cold acclimation significantly increased heparin-releasable LPL ($P<0.05$) and tissue residual LPL ($P<0.01$). Western blot analysis indicated preserved expression of proteins coding for SERCA2, muscle-CPT1 and VLDL-receptor following CA, while AMPK α 2 and phospho-AMPK α 2 were unaffected. These observations indicate that for physiological hypertrophy AMPK phosphorylation does not mediate the enhanced translocation of LPL to cardiac endothelium.

n-3 fatty acids (fish oil) for epilepsy, cardiac risk factors, and risk of SUDEP: clues from a pilot, double-blind, exploratory study²³

OBJECTIVE: The goal of the work described here was to determine the effect of high-dose n-3 fatty acids (eicosapentanoic acid+docosahexanoic acid, fish oil) on several outcomes in subjects with refractory epilepsy, including seizure severity, seizure frequency, cardiac risk factors, and heart rate variability, in a pilot, exploratory planning trial. METHODS: Pilot, randomized, double-blind two-period crossover clinical trial of high-dose fish oil (9600 mg of fish oil/day, 2880 mg of n-3 fatty acids) in 11 subjects with refractory seizures. Outcomes included seizure frequency, seizure severity, lipid panel, and heart rate variability as measured by SDNN and SDANN (defined as the standard deviation of all normal R-R intervals for 1h, and the standard deviation of all R-R intervals in each successive 5-min epoch, respectively). RESULTS: Preliminary data identified trends towards lower seizure severity, lower triglycerides, higher HDL, and increased SDNN/SDANN in those with low SDNN/SDANN at baseline (Spearman's correlation=-0.65, $P=0.03$). No positive effect on seizure frequency was identified. CONCLUSIONS: Further study of the effect of n-3 fatty acids is indicated in people with epilepsy, as favorable trends were identified on cardiac risk factors (triglycerides) and in a subgroup with low heart rate variability (low SDNN/SDANN), a marker of sudden death risk. To our knowledge, this is the first trial to explore the beneficial effects of n-3 fatty acids on cardiac risk factors and heart rate variability in people with epilepsy.

Therapeutic effects of fibrates in postprandial lipemia²⁴

Hypertriglyceridemia is observed in many metabolic diseases such as the metabolic syndrome, diabetes mellitus, or mixed dyslipidemia frequently leading to premature coronary heart disease (CHD). Additionally, several studies have shown that postprandial hypertriglyceridemia is pronounced in patients with CHD, metabolic syndrome, hypertension, and other pathologic conditions. The triglyceride-rich lipoprotein remnants accumulating in the postprandial state seem to be involved in atherogenesis and in events leading to thrombosis. Since abnormal postprandial lipemia is associated with pathologic conditions, its treatment is of clinical importance. Fibrates are of significant help in managing hypertriglyceridemia. This review summarizes the effect of fibric acid derivatives on postprandial lipemia. Fibrates decrease the production of and enhance the catabolism of triglyceride-rich lipoproteins through the activation of peroxisome proliferator-activated receptor- α . Results of clinical studies with fibrates have confirmed their action in decreasing postprandial triglyceride levels by increasing lipoprotein lipase activity, decreasing apolipoprotein CIII production, and by increasing fatty acid oxidation in the liver. It is concluded that fibrates are effective agents in lowering the postprandial increase in remnant lipoprotein particles and retinyl palmitate. Furthermore, fibrates can also affect the postprandial lipid profile by increasing hepatic lipase levels and in some cases, by reducing cholesterol ester transfer protein activity. The main target of fibrate therapy is to improve fasting hypertriglyceridemia, which is an essential component associated with improving postprandial lipemia. Fibrates are well tolerated by patients and adverse effects have been reported rarely after their administration.

Beneficial effect of omega-3 fatty acids on sirolimus- or everolimus-induced hypertriglyceridemia in heart transplant recipients²⁵.

BACKGROUND: Hyperlipidemia is an important complication after organ transplantation and may contribute to the development of posttransplant-accelerated coronary artery disease. Immunosuppressive therapy, especially mammalian target of rapamycin inhibitors, induces a considerable increase in cholesterol and triglyceride plasma levels. Omega-3 fatty acids (FAs) exert cardioprotective effects supporting a therapeutic role in cardiovascular conditions. METHODS: An observational study of omega-3 FAs 4 g/day was performed in 15 heart transplant recipients with hypertriglyceridemia. Six patients received rapamycin, and nine received everolimus. Apart from one patient the immunosuppressive therapy was combined with mycophenolate mofetil, only one patient received steroids; two patients presented with diabetes. RESULTS: Mean triglyceride levels before heart transplantation (HTx) were 137+/-54 mg/dL. After HTx, before sirolimus or everolimus treatment triglyceride level had increased to 188+/-67 mg/dL (P<0.05). Treatment with sirolimus or everolimus induced an increase in triglycerides to 354+/-107 mg/dL (P<0.001). Subsequent treatment with omega-3 FAs for 4 months resulted in a marked decrease in triglycerides to 226+/-74 mg/dL (P<0.001). All patients (100%) showed a reduction in triglyceride by more than 20% (responders). In 10 of 15 patients available 12-month data confirmed the long-term efficacy of omega-3 FAs treatment. There were no adverse events or any discontinuations; no changes in immunosuppression were required. CONCLUSIONS: Treatment with mammalian target of rapamycin inhibitors after HTx induces marked increase in serum levels of triglycerides. Omega-3 FAs significantly lower triglyceride levels and seem to be effective, safe, and well-tolerated in sirolimus- or everolimus-treated heart transplant recipients.

Effects of six APOA5 variants, identified in patients with severe hypertriglyceridemia, on in vitro lipoprotein lipase activity and receptor binding²⁶.

OBJECTIVE: The purpose of this study was to identify rare APOA5 variants in 130 severe hypertriglyceridemic patients by sequencing, and to test their functionality, since no patient recall was possible. METHODS AND RESULTS: We studied the impact in vitro on LPL activity and receptor binding of 3 novel heterozygous variants, apoAV-E255G, -G271C, and -H321L, together with the previously reported -G185C, -Q139X, -Q148X, and a novel construct -Delta139 to 147. Using VLDL as a TG-source, compared to wild type, apoAV-G255, -L321 and -C185 showed reduced LPL activation (-25% [P=0.005], -36% [P<0.0001], and -23% [P=0.02]), respectively). ApoAV-C271, -X139, -X148, and Delta139 to 147 had little effect on LPL activity, but apoAV-X139, -X148, and -C271 showed no binding to LDL-family receptors, LR8 or LRP1. Although the G271C proband carried no LPL and APOC2 mutations, the H321L carrier was heterozygous for LPL P207L. The E255G carrier was homozygous for LPL W86G, yet only experienced severe hypertriglyceridemia when pregnant. CONCLUSIONS: The in vitro determined function of these apoAV variants only partly explains the high TG levels seen in carriers. Their occurrence in the homozygous state, coinheritance of LPL variants or common APOA5 TG-raising variant in trans, appears to be essential for their phenotypic expression.

Update on the use of fibrates: focus on bezafibrate²⁷.

Low-density lipoprotein-cholesterol (LDL-C) is a well established coronary heart disease (CHD) risk factor. However, the ability of this metabolic risk factor alone to identify individuals at risk for future CHD events is limited. The raised triglycerides-low high-density lipoprotein-cholesterol (HDL-C) dyslipidaemia was shown to be an important cardiovascular risk factor independently of LDL-C levels. Fibrates have been used in clinical practice for more than 2 decades as a class of agents known to decrease triglyceride levels while substantially increasing HDL-C levels. Through peroxisome proliferator-activated alpha-receptors, fibrates have a significant impact on the synthesis of several apolipoproteins and enzymes of lipoprotein metabolism as well as on the expression of several genes involved in fibrinolysis and inflammation. Data from recent primary and secondary prevention clinical trials demonstrate the efficacy of fibrate therapy in patients with the raised triglycerides-low HDL-C dyslipidaemia. This review summarizes current data regarding mechanism of action and the metabolic effects of fibrates, as well as results from major clinical trials on the efficacy of this mode of lipid lowering therapy. In addition, recent data from subgroup analyses of the Bezafibrate Infarction Prevention trial, demonstrating several important metabolic and long-term cardiovascular effects of bezafibrate therapy, are detailed.

APOA5 Ala315>Val, identified in patients with severe hypertriglyceridemia, is a common mutation with no major effects on plasma lipid levels²⁸.

BACKGROUND: The importance of the apolipoprotein A5 (APOA5) gene in determining plasma triglyceride (TG) levels has been demonstrated in transgenic and knockout mice and confirmed by human association studies in different ethnic groups. METHODS: We screened for nonsynonymous APOA5 mutations in patients with plasma TG levels >10 mmol/L. The coding sequence and promoter region of the APOA5 gene were sequenced in 95 individuals with severe hypertriglyceridemia (HTG). A large population sample of 3,202 individuals was screened by PCR and restriction analysis for presence of detected mutation. RESULTS: In total, three heterozygous carriers of 944C>T (Ala315>Val) were identified in the severe

HTG patients, while 22 carriers were identified in the population sample. The rare allele frequency of the Val315 was significantly higher in the HTG sample than in controls (0.016 vs. 0.003, $p < 0.01$, respectively). Most of the control Ala315Val carriers, however, had plasma lipid levels (TGs, total cholesterol and high-density lipoprotein cholesterol) within the usual range detected in the population. **CONCLUSIONS:** APOA5 Ala315>Val does not play any dominant/important role in the genetic determination of plasma TG levels, but the increased frequency in HTG patients compared to controls suggests that it might interact with other gene variants to cause HTG.

Management of dyslipidaemia - evidence and practical recommendations²⁹

BACKGROUND: Dyslipidaemia is a common condition managed in general practice. **OBJECTIVE:** This article reviews the evidence and gives practical advice for the management of dyslipidaemia in general practice. **DISCUSSION:** It is essential to identify people at risk of cardiovascular disease (CVD) and to instigate appropriate treatment strategies. An assessment of absolute risk is the most appropriate method of identifying those at a higher risk of CVD where CVD is not overt. People with an absolute risk of >15% of a cardiovascular event in the next 5 years should be actively treated. Drug therapy should also be considered in those estimated to be at 10-15% risk of a cardiovascular event in the next 5 years if they have additional risk factors. It is important to select an appropriate lipid lowering therapy (or combination of drugs) in order to reach lipid targets, which need to consider not just LDL-c but also HDL-c and triglycerides. Lifestyle management should underpin all lipid management strategies.

Triglyceride profile in dyslipidaemia of type 2 diabetes mellitus³⁰

OBJECTIVE: To evaluate ratios of serum triglycerides and cholesterol levels which may indicate postprandial lipid handling and to assess their role as prospective markers of dyslipidaemia in type 2 diabetes mellitus. **STUDY DESIGN:** Comparative, observational study. **PLACE AND DURATION OF STUDY:** Bismillah Taque Hospital, Karachi from July 2002 till December 2003. **PATIENTS AND METHODS:** The study comprised 160 subjects, including 83 known type 2 diabetics (45 males, 38 females) and 77 age-matched controls (45 males, 32 females). Fasting blood samples were analysed for serum triglycerides and total cholesterol, using automated chemistry analyzer. HDL-C was determined by precipitation method and LDL-C and VLDL-C were estimated by Friedewalds formula. LDL/HDL ratio and TG/HDL ratios were also calculated. The mean values for male and female diabetics were compared with that for the male and female non-diabetics respectively and tested for significance by paired t-test. **RESULTS:** Serum triglycerides and VLDL were raised in both male and female diabetics. No significant differences were observed in levels of serum total cholesterol, LDL, HDL and the LDL/HDL ratio. The mean value of the TG/HDL ratio for male diabetics was higher than that for the male non-diabetics ($p = 0.39$). A statistically significant difference was found in the TG/HDL ratios for the female diabetics and non-diabetics ($p < 0.05$). **CONCLUSION:** In this study, type 2 diabetics showed marked hypertriglyceridaemia and raised TG/HDL ratio. The dyslipidaemia of diabetes predisposes to development of coronary heart disease and, therefore, evaluation of the TG:HDL ratio may provide a good tool to monitor and manage the lipid abnormalities in diabetics.

Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men³¹

Both (n-3) long-chain PUFA (LCPUFA) and linoleic acid [LA, 18:2(n-6)] improve cardiovascular disease (CVD) risk factors, but a high-LA intake may weaken the effect of (n-3) LCPUFA. In a controlled, double-blind, 2 x 2-factorial 8-wk intervention, we investigated whether fish oil combined with a high- or low-LA intake affects overall CVD risk profile. Healthy men ($n = 64$) were randomized to 5 mL/d fish oil capsules (FO) [mean intake 3.1 g/d (n-3) LCPUFA] or olive oil capsules (control) and to oils and spreads with either a high (S/B) or a low (R/K) LA content, resulting in a 7.3 g/d higher LA intake in the S/B groups than in the R/K groups. Diet, (n-3) LCPUFA in peripheral blood mononuclear cells, blood pressure (BP), heart rate (HR), and plasma CVD risk markers were measured before and after the intervention. FO lowered fasting plasma triacylglycerol (TAG) ($P < 0.001$) by 51% and 19% in the FO+R/K-group and FO+S/B-group, respectively, which was also reflected in postprandial TAG measured after the intervention ($P < 0.01$). Although a fat x FO interaction was found for monocyte chemoattractant protein-1, neither the FO nor fat intervention affected fasting plasma cholesterol, glucose, insulin, fibrinogen, C-reactive protein, interleukin-6, vascular cell adhesion molecule-1, P-selectin, oxidized LDL, cluster of differentiation antigen 40 ligand (CD40L), adiponectin, or fasting or postprandial BP or HR after adjustment for body weight changes. In conclusion, neither fish oil supplementation nor the LA intake had immediate pronounced effects on the overall CVD risk profile in healthy men, but fish oil lowered plasma TAG in healthy subjects with initially low concentrations.

The ageing male heart: myocardial triglyceride content as independent predictor of diastolic function³²

AIMS: In animal models of obesity and diabetes mellitus, myocardial TG accumulation is associated with decreased myocardial function. In the physiologically ageing heart, myocardial triglyceride (TG) accumulation may also occur due to reduced myocardial fatty acid oxidation. The role of myocardial TG in the ageing human heart is unknown. Therefore, the purpose of our study was to evaluate the effects of ageing on myocardial TG content, and to determine the association

between myocardial TG content and heart function. **METHODS AND RESULTS:** 1H-magnetic resonance spectroscopy and magnetic resonance imaging of the heart were performed in 43 healthy male subjects. Mean age (range) of the subjects was 44 (20-66) years. Body mass index (BMI), blood pressure, and biochemical markers were determined. Age correlated significantly to myocardial TG content ($r = 0.57$, $P < 0.05$) independently of BMI. Furthermore, myocardial TG content correlated negatively with left ventricular diastolic function (represented by E/A ratio, $r = -0.68$, $P < 0.05$). Multivariable analysis indicated myocardial TG content as independent predictor ($P < 0.05$) of the age related decrease in diastolic heart function. **CONCLUSION:** Myocardial TG content increases in the physiologically ageing male heart and is associated with the age-related decline in diastolic function, independent of BMI, blood pressure, and biochemical blood markers.

How Inducing Covariation in Simulated HDL-C, Triglyceride, and Total Cholesterol Data Affects Framingham Risk Equation Results³³.

Objective: To assess the effect of inducing covariation among simulated high-density lipoprotein (HDL-C), triglyceride, and total cholesterol values on Framingham risk equation results. **Methods:** National Health and Nutrition Examination Survey (NHANES) data were used to estimate means and standard deviations for HDL-C, triglyceride, and total cholesterol for all Type II diabetic patients ($N = 293$) and patients with metabolic syndrome ($N = 2303$). NHANES data were also used to estimate correlations between HDL-C, triglyceride, and total cholesterol. Data were simulated and bootstrapped for 1000 replications of the numbers of patients in NHANES. Four-year risks of coronary heart disease were estimated using the Framingham risk equation that includes a nonlinear Weibull function. The differences in means, with and without correlation, were compared to zero to determine whether not inducing correlation was associated with bias. The ratios of variances with and without correlation were compared to one to determine whether not inducing correlation was associated with a different level of precision. All simulation results were compared with bootstrapping results. **Results:** Bootstrapping maintained the correlation in the original data. Inducing correlation leads to more precise estimates that are closer to the bootstrapped estimates for Framingham equations not including triglycerides. Using the Framingham equation for women with triglycerides, the correlated simulation data produce less precise estimates than the uncorrelated data; the uncorrelated data are more precise than the bootstrapped results. **Conclusion:** Not inducing correlation can affect results that combine multiple simulated parameters using nonlinear functions. Researchers engaged in modeling should consider the value of inducing correlation in their simulated data.

Comparison of the safety and efficacy of a combination tablet of niacin extended release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study)³⁴.

The efficacy and safety of 2 regimens of a combination of a proprietary niacin extended release plus simvastatin (NER/S; 1,000/20 and 2,000/20 mg/day) were compared with simvastatin monotherapy (20 mg/day) for 24 weeks in 319 high-risk patients with predominantly mixed dyslipidemia who were already at National Cholesterol Education Program Adult Treatment Panel III risk-adjusted goals for low-density lipoprotein cholesterol. After a run-in on simvastatin 20 mg/day, both NER/S doses (1,000/20 and 2,000/20 mg/day) resulted in greater decreases in non-high-density lipoprotein (HDL) cholesterol vs simvastatin 20 mg/day (-13.9% and -22.5% vs -7.4%, respectively; $p < 0.01$). Significant improvements in HDL cholesterol, triglycerides, apolipoprotein B, lipoprotein(a), and total/HDL cholesterol ratio were also observed. Patients with hypertriglyceridemia (triglycerides $> \text{or} = 200$ mg/dl) typically had greater lipid responses to NER/S with the notable exception that HDL cholesterol responses to NER/S were similar in those with or without increased triglycerides. Treatment with both doses of NER/S was well tolerated; $< \text{or} = 60\%$ of patients in any treatment group experienced flushing, $>90\%$ of flushing was mild or moderate in intensity, and only 7.5% of patients in both NER/S treatment groups discontinued because of flushing. The safety of NER/S was consistent with the safety profile of each individual component. In conclusion, this study showed that NER/S provided additional clinically relevant improvements in multiple lipid parameters and was safe and well tolerated.

The benefit of medium-chain triglyceride therapy on the cardiac function of SHR is associated with a reversal of metabolic and signaling alterations³⁵.

The spontaneously hypertensive rat (SHR) is a model of cardiomyopathy that displays a genetic defect in cardiac fatty acid (FA) translocase/CD36, a plasma membrane long-chain FA transporter. Therapy with medium-chain FAs, which do not require CD36-facilitated transport, has been shown to improve cardiac function and hypertrophy in SHRs despite persistent hypertension. However, little is known about the underlying molecular mechanisms. The aim of this study was to document the impact of medium-chain triglyceride (MCT) therapy in SHRs on the expression level and activity of metabolic enzymes and signaling pathways. Four-week-old male SHRs were administered MCT (SHR-MCT) or long-chain triglyceride (SHR-LCT) for 16 wk. We used Wistar-Kyoto (WKY) rats as controls (WKY-MCT and WKY-LCT). The SHR-MCT group displayed improved cardiac dysfunction [as assessed by left ventricular (LV) end-diastolic pressure and the positive and negative first derivatives of LV pressure/P value], a shift in the beta-myosin heavy chain (MHC)-to-alpha-MHC ratio, and cardiac hypertrophy compared with the SHR-LCT group without an effect on blood pressure. Administration of MCT of SHRs reversed the LCT-induced reduction in the cardiac FA metabolic enzymatic activities of long-chain 3-hydroxyacyl-CoA

dehydrogenase (LCHAD) and medium-chain acyl-CoA dehydrogenase (MCAD). In the SHR-MCT group, the protein expression and transcriptional regulation of myocardial peroxisome proliferator-activated receptor- α , which regulates the transcription of LCHAD and MCAD genes, corresponded to the changes seen in those enzymatic activities. Furthermore, MCT intake caused an inhibition of JNK activation in SHR hearts. Collectively, the observed changes in the myocardial activity of metabolic enzymes and signaling pathways may contribute to the improved cardiac dysfunction and hypertrophy in SHRs following MCT therapy.

Natural honey and cardiovascular risk factors; effects on blood glucose, cholesterol, triacylglycerole, CRP, and body weight compared with sucrose³⁶.

It has been found that honey ameliorates cardiovascular risk factors in healthy individuals and in patients with elevated risk factors. The present study investigated the effect of natural honey on total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triacylglycerole, C-reactive protein (CRP), fasting blood glucose (FBG), and body weight in overweight individuals. There were 55 patients, overweight or obese, who were randomly recruited into the study and assigned into two groups: control group (17 subjects) and experimental group (38 subjects). Patients in the control group received 70 g of sucrose daily for a maximum of 30 days and patients in the experimental group received 70 g of natural honey for the same period. In the control and experimental groups, body weight, body mass index, body fat weight, total cholesterol, LDL-C, HDL-C, triacylglycerole, FBG, and CRP were measured before treatment and at day 31 after the commencement of treatment. Results showed that honey caused a mild reduction in body weight (1.3%) and body fat (1.1%). Honey reduced total cholesterol (3%), LDL-C (5.8), triacylglycerole (11%), FBG (4.2%), and CRP (3.2%), and increased HDL-C (3.3%) in subjects with normal values, while in patients with elevated variables, honey caused reduction in total cholesterol by 3.3%, LDL-C by 4.3%, triacylglycerole by 19%, and CRP by 3.3% ($p < 0.05$). It is our conclusion that consumption of natural honey reduces cardiovascular risk factors, particularly in subjects with elevated risk factors, and it does not increase body weight in overweight or obese subjects.

Effectiveness of a fenofibrate 145-mg nanoparticle tablet formulation compared with the standard 160-mg tablet in patients with coronary heart disease and dyslipidemia³⁷.

STUDY OBJECTIVE: To compare the effectiveness of a fenofibrate 145-mg nanoparticle tablet formulation with the standard 160-mg tablet in patients with dyslipidemia and coronary heart disease. **DESIGN:** Retrospective medical record review. **SETTING:** Outpatient university-affiliated cardiology clinic. **PATIENTS:** One hundred thirty patients with dyslipidemia and coronary heart disease treated for a minimum of 6 months with fenofibrate 160 mg/day (with or without 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor [statin] therapy) who were then switched to a minimum of 3 months of treatment with fenofibrate 145 mg/day. **MEASUREMENTS AND MAIN RESULTS:** Low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglyceride levels were compared during treatment with each formulation. In patients not taking statins, statistically significant reductions of 4.6% and 2.3%, respectively, were noted in mean triglyceride and LDL levels after the switch to fenofibrate 145 mg/day. In patients taking statins, statistically significant reductions of 5.1% and 2.8%, respectively, were observed in mean triglyceride and LDL levels. In total, a larger proportion of patients had 10% or greater improvement in LDL (14/130 [11%]) and triglyceride (32/130 [25%]) levels compared with the proportion of patients who had 10% or greater worsening in LDL (3/130 [2%]) and triglyceride (9/130 [7%]) levels, and a net additional 14 patients (11%) achieved National Cholesterol Education Program (NCEP) lipid panel targets after the switch to fenofibrate 145 mg/day. Mean HDL level was not significantly different after the switch to fenofibrate 145 mg/day. Safety parameters of fenofibrate 145-mg/day therapy were not examined, although fenofibrate 160 mg/day is generally well tolerated. **CONCLUSION:** Eleven percent of the patients in our study had improvements in their lipid profiles that resulted in achievement of NCEP lipid panel targets after treatment with the 145-mg nanoparticle formulation of fenofibrate. This improvement in lipid levels may have been related to increased bioavailability of the 145-mg formulation. However, the exact mechanism of the improvement in lipid levels is unknown.

Effects of modifying triglycerides and triglyceride-rich lipoproteins on cardiovascular outcomes³⁸.

Elevated levels of triglycerides (and triglyceride-rich lipoproteins) are increasingly being recognized as treatment targets to lower cardiovascular risk in certain patient subgroups, including individuals receiving HMG-CoA reductase inhibitors (statins). Evidence suggests that these agents reduce the risk of coronary events more markedly in patients with elevated triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C). Further, intensive long-term statin therapy that reduces both low-density lipoprotein cholesterol (LDL-C) to <70 mg/dL and triglycerides to <150 mg/dL results in a decreased risk of cardiovascular events compared with more moderate statin treatment. Long-term therapy with fibric-acid derivatives, which lower triglycerides and raise HDL-C, appears to reduce mortality in patients with elevated triglycerides and/or those experiencing the most marked reductions in triglycerides on therapy. However, randomized clinical trials involving fibrates have not shown consistent benefit. Niacin (nicotinic acid), which is the most effective available medication for raising HDL-C and also lowers triglycerides, has not been as extensively studied as fibrates in long-term randomized controlled trials. Initial reports (eg, Coronary Drug Project) demonstrated a reduction in coronary disease but not total

mortality in patients randomized to niacin. However, a 15-year follow-up demonstrated that all-cause mortality was significantly reduced in those initially randomized to niacin. At the pathophysiologic level, elevated triglycerides and triglyceride-rich lipoproteins are recognized as potential factors in driving atherosclerotic progression, particularly in mild-to-moderate lesions. Elevated triglycerides also constitute a plausible therapeutic target in certain patients with coronary heart disease (and/or insulin resistance) but without profound LDL-C elevations. The foregoing and other evidence has led consensus panels to lower the upper limit for "normal" triglycerides to 150 mg/dL. Adequately powered randomized controlled trials that specifically assess the effects of lowering triglycerides and raising HDL-C, and trials that target individuals with high triglycerides and low HDL-C, may provide data for recommending specific treatment targets for triglycerides and HDL-C, as well as effective and well-tolerated therapies to achieve these goals.

Omega-3 fatty acid concentrates in the treatment of moderate hypertriglyceridemia³⁹.

BACKGROUND: Moderate hypertriglyceridemia is fairly common, and elevated triglycerides are a risk factor for coronary heart disease. The omega-3 fatty acids EPA and DHA have been shown to lower triglycerides in many clinical studies. Prescription omega-3 fatty acid concentrates (P-OM3) are indicated for use in people with very high triglycerides (> 500 mg/dl). Current guidelines recommend that triglycerides should be less < 150 mg/dl. **OBJECTIVE:** This review provides an overview of the use of omega-3 concentrates (both P-OM3 and over-the-counter fish oil) to lower triglycerides in people who have moderate hypertriglyceridemia (triglycerides in the range of 150 - 500 mg/dl). The objectives were to examine clinical evidence, describe the magnitude of effects and predict future clinical use of P-OM3. **METHODS:** Published, peer-reviewed studies of omega-3 concentrates were included if they were placebo-controlled, double-blind, of sufficient size to demonstrate triglyceride lowering, and studied a population described as having a mean baseline triglyceride value of 150 - 500 mg/dl. Studies using the 4-g dose of P-OM3 were used to develop a model of percent triglyceride lowering as a function of baseline levels. **RESULTS/CONCLUSIONS:** P-OM3 are effective in reducing triglycerides by approximately 30% in this population and are likely to be combined with other drugs (e.g., statins) to treat combined dyslipidemia.

Abnormal Igf2 gene in Prague hereditary hypertriglyceridemic rats: its relation to blood pressure and plasma lipids

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Prague hypertriglyceridemic (HTG) rats represent a suitable model of metabolic syndrome. We have established the set of F(2) hybrids derived from HTG and Lewis progenitors to investigate the relationship between respective polymorphism(s) of Igf2 gene and blood pressure (BP) or other cardiovascular phenotypes. HTG rats had elevated systolic BP and plasma triglycerides but lower plasma cholesterol compared to Lewis rats of both genders. In males, there was higher mean arterial pressure, diastolic BP and relative heart weight in HTG than in Lewis rats. The results obtained in the total population of F(2) hybrids indicated strong segregation of Igf2 genotype with plasma triglycerides. There was no segregation of Igf2 genotype with any BP component except BP changes occurring after the blockade of either renin-angiotensin system (RAS) or NO synthase. When F(2) population was analyzed according to gender, male F(2) progeny homozygous for HTG Igf2 allele had significantly higher plasma triglycerides and greater BP changes after NO synthase blockade than those homozygous for Lewis allele. On the contrary, male F(2) progeny homozygous for HTG Igf2 allele had significantly lower plasma cholesterol and smaller BP changes after RAS blockade. PCR analysis of Igf2 gene by using of microsatellite D1Mgh22 has shown polymorphism between HTG and Lewis rats. Sequence analysis of cDNA revealed insertion of 14 nucleotides in HTG gene. In conclusion, polymorphism in Igf2 gene may be responsible for differences in lipid metabolism between HTG and Lewis rats. It remains to determine how these abnormalities could be involved in BP regulation by particular vasoactive systems.

The functional interaction on in vitro gene expression of APOA5 SNPs, defining haplotype APOA52, and their paradoxical association with plasma triglyceride but not plasma apoAV levels⁴¹.

Plasma triglyceride (TG) and apoAV levels are reported to be positively correlated, yet SNPs defining haplotype APOA52 have consistently shown association with elevated plasma triglyceride (TG) but not plasma apoAV levels. We previously reported that individually -1131T>C, -3A>G and +1891T>C did not influence luciferase activity or in vitro translation efficiency. To investigate the combined effect of these SNPs additional constructs were examined. Compared to the wildtype -1131T/-3A/+1891T (TAT), the triple rare allele construct -1131C/-3G/+1891C (CGC) conferred 46% lower luciferase activity ($p < 0.0001$), showing these SNPs are acting co-operatively. Although only these two combinations occur in vivo, we experimentally altered the TAT construct one site at a time; -3G (TGT) had the largest effect (94% lower luciferase), with lesser effects from CAT (-77%) and TAC (-70.3%) (all $p < 0.0001$). Deletion constructs excluding one site at a time showed that -3G/1891C (-GC) in combination, compared to -AT, was having the largest effect on luciferase activity (-59%, $p = 0.055$). Using sequence homology and EMSA analysis no transcription factor binding at -1131 or +1891 was identified, though +1891 lies within a putative mRNA stability motif. Taken together, these data identify -3A>G in the Kozak sequence as functional, affecting translation initiation and driving the haplotype effects, while showing interaction with +1891T>C and to a lesser extent -1131T>C. A paradox arises since these results predict that APOA52 will lead to reduced apoAV with concomitant reduced LPL activation or lipoprotein-receptor interaction, resulting in higher plasma TG levels. We conclude

that APOA5 expression, and not circulating plasma apoAV levels, is causatively associated with plasma TG levels.

Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study)⁴².

Diabetes mellitus is a strong risk factor for atherosclerosis and is often characterized by dyslipidemia. Besides acting on traditional lipids, statins and fibrates may also exert beneficial effects on various pro- and antiatherogenic lipid subparticles. This analysis was undertaken to evaluate combination therapy on lipid subparticles in the Diabetes and Combined Lipid Therapy Regimen (DIACOR) study. Patients with type 2 diabetes mellitus and no histories of coronary heart disease were evaluated (n = 498). Eligible patients underwent a 6- to 8-week washout period of all lipid-lowering medications and were enrolled if they demonstrated mixed dyslipidemia (having ≥ 2 of the following 3 lipid parameters: low-density lipoprotein [LDL] cholesterol ≥ 100 mg/dl, triglycerides ≥ 200 mg/dl, and high-density lipoprotein cholesterol < 40 mg/dl). Patients were randomized to simvastatin 20 mg, fenofibrate 160 mg, or combined simvastatin 20 mg and fenofibrate 160 mg. Lipid subparticles were assessed 12 weeks after randomization by the Vertical Auto Profile II method. A total of 300 patients (mean age 61.6 \pm 11.5 years, 55% men) were randomized. Combination therapy was superior in lowering LDL cholesterol pattern B (-33.9 mg/dl) and dense very low-density lipoprotein cholesterol (-10.0 mg/dl) and increasing high-density lipoprotein3 (+2.3 mg/dl) and exerted the greatest change in altering the LDL cholesterol size profile. A potential effect on lipoprotein(a) (-0.5 mg/dl) was also found. For those with triglycerides > 170 mg/dl, combination therapy was superior in lowering dense very low density lipoprotein cholesterol (-10.7 mg/dl) and LDL cholesterol pattern B (-35.8 mg/dl), the lipids that tend to be formed in the presence of elevated triglycerides. In conclusion, in this trial of mixed dyslipidemic patients with diabetes, combination therapy was more effective in changing a variety of other cardiovascular risk markers.

Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial⁴³.

OBJECTIVES: The purpose of this study was to assess the impact of on-treatment triglycerides (TG) on coronary heart disease (CHD) risk after an acute coronary syndrome (ACS). **BACKGROUND:** The PROVE IT-TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) 22 trial demonstrated that low-density lipoprotein cholesterol (LDL-C) < 70 mg/dl was associated with greater CHD event reduction than LDL-C < 100 mg/dl after ACS. However, the impact of low on-treatment TG on CHD risk beyond LDL-C < 70 mg/dl has not been explored. **METHODS:** The PROVE IT-TIMI 22 trial evaluated 4,162 patients hospitalized for ACS and randomized to atorvastatin 80 mg or pravastatin 40 mg daily. The relationship between on-treatment levels of TG and LDL-C and the composite end point of death, myocardial infarction (MI), and recurrent ACS were assessed 30 days after initial presentation. **RESULTS:** Low on-treatment TG (< 150 mg/dl) was associated with reduced CHD risk compared with higher TG in univariate analysis (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.62 to 0.87; $p < 0.001$) and in adjusted analysis (HR 0.80, 95% CI 0.66 to 0.97; $p = 0.025$). For each 10-mg/dl decrement in on-treatment TG, the incidence of death, MI, and recurrent ACS was lower by 1.6% or 1.4% after adjustment for LDL-C or non-high-density lipoprotein cholesterol and other covariates ($p < 0.001$ and $p = 0.01$, respectively). Lower CHD risk was also observed with TG < 150 mg/dl and LDL-C < 70 mg/dl (HR 0.72, 95% CI 0.54 to 0.94; $p = 0.017$) or low on-treatment TG, LDL-C, and C-reactive protein (< 2 mg/l) (HR 0.59, 95% CI 0.41 to 0.83; $p = 0.002$) compared with higher levels of each variable in adjusted analysis. **CONCLUSIONS:** On-treatment TG < 150 mg/dl was independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG may be an additional consideration beyond low LDL-C in patients after ACS.

Pure hypertriglyceridemia might be associated with erectile dysfunction: a pilot study⁴⁴.

INTRODUCTION: Unlike the association between erectile dysfunction (ED) and high levels of low-density lipoprotein (LDL) cholesterol, the association between ED and hypertriglyceridemia is still debatable. **Aim.** To study prevalence and severity of ED in young men with very high levels of triglycerides. **MAIN OUTCOME MEASURES:** Prevalence of ED, ED severity, total cholesterol levels, LDL cholesterol levels, and triglycerides levels. **METHODS:** Men who were enrolled went through routine health checks including full lipid profiling and completion of the Sexual Health Inventory for Men (SHIM) questionnaire. Very high levels of triglycerides were defined as ≥ 500 mg/dL. Very high levels of LDL cholesterol were defined as ≥ 190 mg/dL. Men with diabetes, ischemic heart disease, high-density lipoprotein (HDL) cholesterol ≥ 60 mg/dL, and mixed hyperlipidemias were excluded. **RESULTS:** Included were 88 men, aged 35.9 \pm 7.1 years (range: 25-51 years): 21 men with "pure" severe hypertriglyceridemia (triglyceride levels ≥ 500 mg/dL and non-HDL cholesterol < 189 mg/dL), 34 men with "pure" severe hyperlipidemia (LDL cholesterol levels ≥ 190 mg/dL and triglycerides < 199 mg/dL), and 33 men with normal cholesterol levels. No significant differences were found between these groups in terms of mean age and mean SHIM score. Prevalence of ED (i.e., SHIM score < 22) was higher among men with "pure" severe hypertriglyceridemia than among men with "pure" severe hyperlipidemia (42.9% vs. 29.4%) and men with normal cholesterol levels (42.9% vs. 24.2%), although these results were not statistically significant ($P = 0.2$ and 0.4 , respectively). **CONCLUSIONS:** Prevalence of ED might be increased in young men with "pure" severe hypertriglyceridemia, though a larger cohort with a longitudinal

follow-up is needed to prove that hypertriglyceridemia is an independent risk factor for ED.

Effects of total cholesterol and triglyceride on the percentage difference between the low-density lipoprotein cholesterol concentration measured directly and calculated using the Friedewald formula⁴⁵

BACKGROUND: We elucidate how the triglyceride (TG) and total cholesterol (TC) concentrations affect the percentage difference (%DeltaLDL) between the low-density lipoprotein cholesterol (LDL-C) concentration evaluated by direct measurement (DLDL-C) and calculated using the Friedewald formula (FLDL-C), under conditions allowing the calculation. **METHODS:** Serum concentrations of TC, TG, high-density lipoprotein cholesterol (HDL-C), and DLDL-C were measured and the FLDL-C and %DeltaLDL were calculated for 38,243 Koreans who had TG values <4.52 mmol/L. The DLDL-C was measured using the homogeneous Kyowa Medex assay (Kyowa, Tokyo, Japan). The %DeltaLDL was calculated using the equation: [(FLDL-C-DLDL-C)/DLDL-C]x100. **RESULTS:** The mean %DeltaLDL-C was -9.1+/-6.4%. The %DeltaLDL differed by more than +/-5% in 75.4% of the subjects, and the FLDL-C was lower than the DLDL-C in 96.3%. The mean %DeltaLDL-C for the group with the highest TG and lowest TC was 11.8-fold that for the group with the lowest TG and highest TC. **CONCLUSIONS:** Under conditions satisfying the requirements of the Friedewald formula, the DLDL-C and FLDL-C differed significantly over the concentration ranges of both TC and TG. In an evaluation of patients with hyperlipidemia, the Friedewald calculation may underestimate the risk for coronary heart disease.

Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives⁴⁶

The most common omega-3 fatty acids contain 18-22 carbons and a signature double bond at the third position from the methyl (or n, or omega) end of the molecule. These fatty acids must be obtained in the diet as they cannot be synthesized by vertebrates. They include the plant-derived alpha-linolenic acid (ALA, 18:3n-3), and the fish-oil-derived eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). Normally, very little ALA is converted to EPA, and even less to DHA, and therefore direct intake of the latter two is optimal. EPA and DHA and their metabolites have important biologic functions, including effects on membranes, eicosanoid metabolism, and gene transcription. Studies indicate that the use of fish oil is associated with coronary heart disease risk reduction. A number of mechanisms may be responsible for such effects. These include prevention of arrhythmias as well as lowering heart rate and blood pressure, decreasing platelet aggregation, and lowering triglyceride levels. The latter is accomplished by decreasing the production of hepatic triglycerides and increasing the clearance of plasma triglycerides. Our focus is to review the potential mechanisms by which these fatty acids reduce cardiovascular disease risk.

Genetic screening of the LPL gene in hypertriglyceridaemic patients⁴⁷

Serum triglyceride (TG) level is an important independent risk factor for coronary heart disease, with the lipoprotein lipase (LPL) enzyme playing the major role in regulating the catabolism of TG rich lipoproteins. The complete sequence analysis of the LPL gene was carried out on 19 individuals with extreme hypertriglyceridaemia (HTG; TG>14 mmol/l) with a total of 42 sequence variants being identified, a number of which are novel to this study. A total of eight patients were shown to have functional variants (p.D36N, p.R197H, p.N318S, p.V340I) that alter amino acids at 11 of the 16 LPL alleles. Multiplex ligation-dependent probe amplification (MLPA) analysis showed no exonic deletion or duplications in this population. Further analysis of the p.N318S (also called N291S) variant identified in the sequencing screen, in larger case and control populations, identified this mutation to be strongly associated with HTG. This study has produced a more comprehensive SNP map of LPL and its surrounding area and identified p.N318S as a major predisposing factor to HTG in the Northern Irish population.

Moderate exercise reduces serum triacylglycerol concentrations but does not affect pre-heparin lipoprotein lipase concentrations after a moderate-fat meal in young men⁴⁸

Aerobic exercise has been shown to lower postprandial TAG concentrations after a meal(s) of high-fat content. This study examined the effects of moderate-intensity cycling on postprandial TAG concentrations and pre-heparin lipoprotein lipase concentrations after subjects consumed a meal of moderate-fat content (45 % of total energy). Twelve male subjects, aged 24 (sem 1) years, completed two 2 d trials (exercise and control) at least 1 week apart in a randomised, repeated measures design. On day 1, subjects either cycled for 30 min at 65 % of maximum heart rate in the afternoon or rested (no exercise). On day 2 of both trials, after an overnight stay with an 11 h fast, subjects consumed a test meal of moderate-fat content (0.61 g fat, 1.34 g carbohydrate, 0.37 g protein and 51 kJ energy/kg body mass) for breakfast. Blood samples were collected at baseline (before the exercise or at an equivalent time-point during the control trial on day 1), in the fasted state (0 h) and at 2, 4 and 6 h postprandially on day 2. The total and incremental areas under the serum TAG concentration v. time curve were 30 % (P = 0.039) and 33 % (P = 0.012) lower on the exercise trial compared with the control trial, respectively. Serum pre-heparin lipoprotein lipase concentrations did not differ between the exercise and control trials. These findings demonstrate that 30 min of moderate-intensity cycling performed the day before a meal of moderate-fat content is effective at lowering postprandial serum TAG concentrations but does not affect serum pre-heparin lipoprotein lipase concentrations

in young men.

Vascular and metabolic effects of treatment of combined hyperlipidemia: focus on statins and fibrates⁴⁹

Combined hyperlipidemia results from overproduction of hepatically synthesized apolipoprotein B in very low-density lipoproteins in association with reduced lipoprotein lipase activity. Thus, this condition is typically characterized by concurrent elevations in total cholesterol and triglycerides with decreased high-density lipoprotein cholesterol. High levels of apolipoprotein B-containing lipoproteins, most prominently carried by low-density lipoprotein (LDL) particles, are an important risk factor for coronary heart disease. Statin therapy is highly effective at lowering LDL cholesterol. Despite the benefits of statin treatment for lowering total and LDL cholesterol, many statin-treated patients still have initial or recurrent coronary heart disease events. In this regard, combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than either drug alone. Furthermore, statins and fibrates activate PPARalpha in a synergistic manner providing a molecular rationale for combination treatment in coronary heart disease. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance so that there may also be additional beneficial metabolic effects of combined statin/fibrates therapy. However, there has been little published evidence that combined therapy is synergistic or even better than monotherapy alone in clinical studies. Therefore, there is a great need to study the effects of combination therapy in patients. When statins are combined with gemfibrozil therapy, this is more likely to be accompanied by myopathy. However, this limitation is not observed when fenofibrate, bezafibrate, or ciprofibrate are used in combination therapy.

Association of serum lipid indices with large artery atherosclerotic stroke⁵⁰

BACKGROUND: Low-density lipoprotein cholesterol (LDL) is the primary lipid target for vascular risk reduction in stroke patients, but emerging data suggest that other lipid indices may better predict vascular hazard. We evaluated the relationship between several measures of the classically obtained serum lipid panel and the occurrence of large artery atherosclerotic stroke. **METHODS:** Data prospectively collected over a 4-year period on subjects admitted with ischemic stroke or TIA to a university medical center were analyzed. Independent associations of fasting serum lipid indices with large artery atherosclerotic (LAA) stroke mechanism were evaluated. **RESULTS:** Of 1,049 patients, 247 (23.5%) were classified with LAA, 224 (21.4%) were classified with small vessel disease (SVD), and 578 (55%) were non-LAA, non-SVD subtype. Lipid levels were similar between LAA and SVD patients. Total cholesterol, triglycerides, LDL, non-high-density lipoprotein cholesterol (HDL), and triglyceride:HDL ratio were significantly higher in LAA vs non-LAA, non-SVD patients. After adjustment for age, hypertension, diabetes, smoking, body mass index, and premorbid statin use, significant odds ratios (ORs) for LAA compared with all other ischemic stroke subtypes for patients in the uppermost lipid quartiles (vs lowest) were triglycerides (OR 2.69, 95% CI 1.44 to 5.02) and non-HDL (OR 2.39, 95% CI 1.40 to 4.11). LDL was not associated with LAA. **CONCLUSIONS:** Compared with all other ischemic stroke subtypes, elevated levels of serum triglycerides and non-high-density lipoprotein, but not low-density lipoprotein (LDL), are associated with large artery atherosclerotic stroke. These non-LDL lipid measures may have utility in delineating atherosclerotic stroke risk.

Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women⁵¹

CONTEXT: The association of triglycerides with incident cardiovascular disease remains controversial. Although triglyceride levels are typically obtained in the fasting state, postprandial hypertriglyceridemia may play an important role in atherosclerosis. **OBJECTIVE:** To determine the association of triglyceride levels (fasting vs nonfasting) and risk of future cardiovascular events. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective study of 26,509 initially healthy US women (20,118 fasting and 6391 nonfasting) participating in the Women's Health Study, enrolled between November 1992 and July 1995 and undergoing follow-up for a median of 11.4 years. Triglyceride levels were measured in blood samples obtained at time of enrollment. **MAIN OUTCOME MEASURE:** Hazard ratios for incident cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death). **RESULTS:** At baseline, triglyceride levels in fasting as well as nonfasting women correlated with traditional cardiac risk factors and markers of insulin resistance. During a median follow-up of 11.4 years, 1001 participants experienced an incident cardiovascular event (including 276 nonfatal myocardial infarctions, 265 ischemic strokes, 628 coronary revascularizations, and 163 cardiovascular deaths), for an overall rate of 3.46 cardiovascular events per 1000 person-years of follow-up. After adjusting for age, blood pressure, smoking, and use of hormone therapy, both fasting and nonfasting triglyceride levels predicted cardiovascular events. Among fasting participants, further adjustment for levels of total and high-density lipoprotein cholesterol and measures of insulin resistance weakened this association (fully adjusted hazard ratio [95% confidence interval] for increasing tertiles of triglyceride levels: 1 [reference], 1.21 [0.96-1.52], and 1.09 [0.85-1.41] [P = .90 for trend]). In contrast, nonfasting triglyceride levels maintained a strong independent relationship with cardiovascular events in fully adjusted models (hazard ratio [95% confidence interval] for increasing tertiles of levels: 1 [reference], 1.44 [0.90-2.29], and 1.98 [1.21-3.25] [P = .006 for trend]). In secondary analyses stratified by time since participants' last meal, triglyceride levels measured 2 to 4 hours postprandially had the strongest association with cardiovascular events (fully adjusted hazard ratio [95% confidence interval] for highest vs lowest tertiles of levels, 4.48 [1.98-10.15] [P < .001 for trend]), and this association

progressively decreased with longer periods of fasting. **CONCLUSIONS:** In this cohort of initially healthy women, nonfasting triglyceride levels were associated with incident cardiovascular events, independent of traditional cardiac risk factors, levels of other lipids, and markers of insulin resistance; by contrast, fasting triglyceride levels showed little independent relationship.

Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women⁵²

CONTEXT: Elevated nonfasting triglycerides indicate the presence of remnant lipoproteins, which may promote atherosclerosis. **OBJECTIVE:** To test the hypothesis that very high levels of nonfasting triglycerides predict myocardial infarction (MI), ischemic heart disease (IHD), and death. **DESIGN, SETTING, AND PARTICIPANTS:** A prospective cohort study of 7587 women and 6394 men from the general population of Copenhagen, Denmark, aged 20 to 93 years, followed up from baseline (1976-1978) until 2004. **MAIN OUTCOME MEASURES:** Hazard ratios (HRs) for incident MI, IHD, and total death according to baseline nonfasting triglyceride level categories of 1 to 1.99 mmol/L (88.5-176.1 mg/dL), 2 to 2.99 mmol/L (177.0-264.6 mg/dL), 3 to 3.99 mmol/L (265.5-353.0 mg/dL), 4 to 4.99 mmol/L (354.0-441.6 mg/dL), and 5 mmol/L or more ($>$ or $=$ 442.5 mg/dL) vs triglyceride levels of less than 1 mmol/L ($<$ 88.5 mg/dL). **RESULTS:** With increasing levels of nonfasting triglycerides, levels of remnant lipoprotein cholesterol increased. During a mean follow-up of 26 years, 1793 participants (691 women and 1102 men) developed MI, 3479 (1567 women and 1912 men) developed IHD, and 7818 (3731 women and 4087 men) died. For MI, among women, the age-adjusted HRs and multifactorially adjusted HRs (aHRs) for each respective category per 1-mmol/L increase in nonfasting triglyceride levels were 2.2 (aHR, 1.7), 4.4 (aHR, 2.5), 3.9 (aHR, 2.1), 5.1 (aHR, 2.4), and 16.8 (aHR, 5.4); for both, P for trend $<$.001. For MI, among men, the values were 1.6 (aHR, 1.4), 2.3 (aHR, 1.6), 3.6 (aHR, 2.3), 3.3 (aHR, 1.9), and 4.6 (aHR, 2.4); for both, P for trend $<$.001. For IHD, among women, the values were 1.7 (aHR, 1.4), 2.8 (aHR, 1.8), 3.0 (aHR, 1.8), 2.1 (aHR, 1.2), and 5.9 (aHR, 2.6); for both, P for trend $<$.001. For IHD, among men, the values were 1.3 (aHR, 1.1), 1.7 (aHR, 1.3), 2.1 (aHR, 1.3), 2.0 (aHR, 1.2), and 2.9 (aHR, 1.5); P for trend $<$.001 for age-adjusted and P for trend = .03 for multifactorially adjusted. For total death, among women, the values were 1.3 (aHR, 1.3), 1.7 (aHR, 1.6), 2.2 (aHR, 2.2), 2.2 (aHR, 1.9), and 4.3 (aHR, 3.3); for both, P for trend $<$.001. For total death, among men, the values were 1.3 (aHR, 1.2), 1.4 (aHR, 1.4), 1.7 (aHR, 1.5), 1.8 (aHR, 1.6), and 2.0 (aHR, 1.8); for both, P for trend $<$.001. **CONCLUSION:** In this general population cohort, elevated nonfasting triglyceride levels were associated with increased risk of MI, IHD, and death in men and women.

Mechanisms of disease: lessons from ethnicity in the role of triglyceride metabolism in ischemic heart disease⁵³

Mean risk factor levels in various ethnic groups illustrate the potential importance of triglyceride metabolism in the risk for ischemic heart disease (IHD). Serum triglyceride concentrations are a surrogate for a range of potentially atherogenic disturbances in lipoprotein species, including increased concentrations of remnants of VLDL and chylomicron metabolism, increased small, dense LDL concentrations and reduced HDL concentrations. Differences between at-risk groups in lipoprotein profiles reflect alterations in the metabolism of triglycerides that might be greater than differences observed when only circulating triglyceride concentrations are measured. This atherogenic lipoprotein profile is typically found in association with increased visceral fat, insulin resistance and type 2 diabetes and might be a characteristic of Asian Indian ethnicity. By contrast, despite being relatively insulin resistant, Afro-Caribbean men in the UK have a low risk of IHD and lack the adverse lipoprotein profile. This could result from secretion of relatively large proportions of their VLDL as small, triglyceride-poor particles, levels of which are not augmented in response to loss of insulin action. These considerations re-endorse the potential importance of triglyceride metabolism in IHD and present opportunities for identifying useful areas in which drug targets for reducing IHD risk can be sought.

[Lipids and apolipoproteins A1 and B alterations in stroke]⁵⁴

The purpose of this case-control study was to determine the variations of lipoproteins during stroke in adults from Ivory Coast. The survey included 72 subjects presenting with hemorrhagic stroke and 58 of ischemic stroke, aged of 25 at 93 years. Lipids parameters have been measured by a colorimetric enzymatic method. Apolipoproteins have been determined by immunoturbidimetry. Results showed significant decrease of HDL-cholesterol and apoprotein A1 in patients by comparison with control subjects. More over, an increase of the atherogenicity index expressed as total/HDL-cholesterol or apolipoprotein B /apolipoprotein A1, of the triglycerides and apolipoprotein B has been observed.

Changes in triglyceride levels and risk for coronary heart disease in young men⁵⁵

BACKGROUND: Current triglyceride levels might be only a weak predictor of risk for coronary heart disease (CHD). **OBJECTIVE:** To assess the association between changes over time in fasting triglyceride levels and CHD risk in young adults. **DESIGN:** Follow-up study over 5.5 years after 2 measurements of fasting triglycerides 5 years apart. **SETTING:** The Staff Periodic Examination Center of the Israel Defense Forces, Zrifin, Israel. **PATIENTS:** 13,953 apparently healthy, untreated, young men (age 26 to 45 years) with triglyceride levels less than 3.39 mmol/L ($<$ 300 mg/dL). **MEASUREMENTS:** Two triglyceride measurements (at enrollment [time 1] and 5 years later [time 2]), lifestyle variables, and incident cases of

angiography-proven CHD. RESULTS: Within 5.5 years, 158 new cases of CHD were identified. The multivariate model was adjusted for age; family history; fasting glucose; high-density lipoprotein cholesterol; blood pressure; body mass index; and changes between time 1 and time 2 in body mass index, physical activity, smoking status, and habit of eating breakfast. Investigators categorized triglyceride levels according to low, intermediate, and high tertiles (as measured at time 1 and time 2 [expressed as tertile at time 1/tertile at time 2]). The risk for CHD in men with high-tertile triglyceride levels at time 1 changed depending on the tertile at time 2 (hazard ratios, 8.23 [95% CI, 2.50 to 27.13] for high/high, 6.84 [CI, 1.95 to 23.98] for high/intermediate, and 4.90 [CI, 1.01 to 24.55] for high/low, compared with the stable low/low group). The risk for CHD in men with low-tertile levels at time 1 also changed depending on the tertile at time 2 (hazard ratios, 3.81 [CI, 0.96 to 15.31] for low/intermediate and 6.76 [CI, 1.34 to 33.92] for low/high, compared with the stable low/low group). LIMITATIONS: Participants were healthy and had a low incidence rate of CHD. The study was observational. CONCLUSIONS: Two triglyceride measurements obtained 5 years apart may assist in assessing CHD risk in young men. A decrease in initially elevated triglyceride levels is associated with a decrease in CHD risk compared with stable high triglyceride levels. However, this risk remains higher than in those with persistently low triglyceride levels.

Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome⁵⁶.

OBJECTIVE: The aim of this study was to determine the effects of fenofibrate (160 mg/day) on fasting and postprandial lipoproteins, oxidized fatty acids, and inflammatory mediators in subjects with hypertriglyceridemia and the metabolic syndrome. RESEARCH DESIGN AND METHODS: Fifty-nine subjects with fasting hypertriglyceridemia (≥ 1.7 and < 6.9 mmol/l) and two or more of the Adult Treatment Panel III criteria for the metabolic syndrome were randomly assigned to fenofibrate (160 mg/day) or placebo in a double-blind, controlled clinical trial. RESULTS: Fenofibrate treatment lowered fasting triglycerides (-46.1%, $P < 0.0001$) and postprandial (area under the curve) triglycerides (-45.4%, $P < 0.0001$) due to significant reductions in postprandial levels of large (-40.8%, $P < 0.0001$) and medium (-49.5%, $P < 0.0001$) VLDL particles. The number of fasting total LDL particles was reduced in fenofibrate-treated subjects (-19.0%, $P = 0.0033$) primarily due to reductions in small LDL particles (-40.3%, $P < 0.0001$); these treatment differences persisted postprandially. Fasting and postprandial oxidized fatty acids were reduced in fenofibrate-treated subjects compared with placebo-administered subjects (-15.3%, $P = 0.0013$, and 31.0%, $P < 0.0001$, respectively), and fenofibrate therapy lowered fasting and postprandial soluble vascular cell adhesion molecule-1 (VCAM-1) (-10.9%, $P = 0.0005$, and -12.0%, $P = 0.0001$, respectively) as well as fasting and postprandial soluble intercellular adhesion molecule-1 (ICAM-1) (-14.8%, $P < 0.0001$, and -15.3%, $P < 0.0001$, respectively). Reductions in VCAM-1 and ICAM-1 were correlated with reductions in fasting and postprandial large VLDL particles ($P < 0.0001$) as well as postprandial oxidized fatty acids ($P < 0.0005$). CONCLUSIONS: Triglyceride-lowering therapy with fenofibrate reduced fasting and postprandial free fatty acid oxidation and inflammatory responses, and these antiatherosclerotic effects were most highly correlated with reductions in large VLDL particles.

Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study⁵⁷.

BACKGROUND: The Helsinki Heart Study was a double-blind, placebo-controlled primary prevention trial among 4081 dyslipidemic middle-aged men to test the efficacy of gemfibrozil in the prevention of coronary heart disease (CHD). After the 5-year trial, the participants were notified of their treatment group and invited to continue or start gemfibrozil therapy free of charge through 1995. Approximately two thirds of participants in both groups chose gemfibrozil therapy. In this 18-year follow-up through 2000, we compared the CHD, cancer, and all-cause mortality among subjects in the original gemfibrozil (OG) group ($n = 2046$) with those in the original placebo (OP) group ($n = 2035$). METHODS: To provide an overview of the absolute risks in the 2 treatment groups as well as risk differences between them, we calculated crude mortality rates and presented Kaplan-Meier plots of survival with log-rank tests. We also estimated the relative risks (RRs) using Cox proportional hazards models with and without covariates. RESULTS: During the follow-up until 1995, subjects in the OG group had a 32% lower RR of CHD mortality ($P = .03$) compared with those in the OP group, and when followed up until 2000, the RR was 23% lower ($P = .05$). Overall, there were no differences in all-cause or cancer mortality. However, those in the OG group with both body mass index and triglyceride level in the highest tertiles had a 71% lower RR of CHD mortality ($P < .001$), a 33% lower RR of all-cause mortality ($P = .03$), and a 36% lower RR of cancer mortality ($P = .22$) compared with those in the OP group. CONCLUSION: Long-term mortality follow-up showed that patients with dyslipidemia benefited from beginning treatment with gemfibrozil early, especially if their dyslipidemia entailed factors related to the metabolic syndrome.

The triglyceride-lowering effects of a modest dose of docosahexaenoic acid alone versus in combination with low dose eicosapentaenoic acid in patients with coronary artery disease and elevated triglycerides⁵⁸.

BACKGROUND: Hypertriglyceridemia is a risk factor for coronary artery disease (CAD). The American Heart Association recommends 1000 mg of omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), daily for cardioprotection and higher doses for triglyceride-lowering in patients with CAD. METHODS: This was a prospective, randomized, double-blind study comparing DHA to DHA + EPA in patients with CAD and triglycerides greater than 200

mg/dL. Subjects were randomized to either 1000 mg of DHA or 1252 mg of DHA + EPA for eight weeks. Baseline and eight-week laboratories were drawn to assess changes in the fasting lipid profile. The primary objective was to evaluate the change in triglycerides between the two groups at eight weeks. RESULTS: A total of 116 subjects were enrolled; 57 in the DHA group and 59 in the DHA + EPA group. Baseline characteristics were similar between groups. The mean age was 69.4 +/- 9.1 years and 70.7% were male. Triglycerides decreased by an average of 21.8% in the DHA group ($p < 0.001$) and 18.3% in the DHA + EPA group ($p < 0.001$). The difference between groups was not significant. A greater proportion of subjects in the DHA group achieved triglyceride goal (less than 150 mg/dL) compared to the DHA + EPA group (24.6% versus 10.2%, $p < 0.05$). CONCLUSIONS: Our results indicate that the American Heart Association recommended cardioprotective dose of omega-3 fatty acids can also significantly lower triglycerides in patients with CAD. There do not appear to be significant differences in triglyceride-lowering between DHA only and DHA + EPA combination products when dosing is based on DHA.

Attenuation of progression of insulin resistance in patients with coronary artery disease by bezafibrate⁵⁹

BACKGROUND: Development of insulin resistance (IR) may be important in the pathogenesis of both metabolic syndrome and type 2 diabetes mellitus. Few data are available regarding the short-term efficacy of the peroxisome proliferator-activated receptor ligand bezafibrate on IR, and its long-term effect is unknown. The present analysis aimed to investigate the effect of bezafibrate on IR in patients with coronary artery disease enrolled in the Bezafibrate Infarction Prevention Study. METHODS: Metabolic and inflammatory parameters were analyzed from stored frozen plasma samples obtained from patients who completed a 2-year, randomized, double-blind, placebo-controlled study. The homeostatic indexes of IR (HOMA-IRs) were calculated according to the homeostasis model of assessment. RESULTS: Both the patients taking bezafibrate ($n = 1262$) and those taking placebo ($n = 1242$) displayed similar baseline characteristics. The HOMA-IRs significantly correlated at baseline and during follow-up with glucose ($r = 0.35$ and 0.31 , respectively) and triglycerides ($r = 0.16$ and 0.19 , respectively). In a subgroup of 351 patients with diabetes, HOMA-IR at baseline was 88% higher than in their counterparts with normal glucose levels ($P < .001$). In the placebo group, during follow-up there was a significant 34.4% rise in HOMA-IR. In contrast, in the bezafibrate group there was only a nonsignificant 6.6% change in HOMA-IR. The intergroup differences in percentage changes of HOMA-IR were in favor of bezafibrate ($P < .001$). CONCLUSIONS: In patients with coronary artery disease enrolled in our study, as represented by the placebo group, HOMA-IR increased over time. During the 2 years of the follow-up, bezafibrate significantly attenuated this process.

HDL-raising strategies in the treatment of coronary artery disease: perspectives from the Armed Forces Regression Study⁶⁰

PURPOSE OF REVIEW: Even with the aggressive reduction of LDL-cholesterol, the risk of cardiovascular events in patients with coronary artery disease remains substantial. The Armed Forces Regression Study was a randomized, double-blind, placebo-controlled trial of combination drug therapy aimed at raising HDL-cholesterol in patients with angiographically evident coronary artery disease. Drug therapy ultimately resulted in regression of the angiographic lesions and a reduction in cardiovascular events. This review places the Armed Forces Regression Study within the context of other recent studies. RECENT FINDINGS: In the past few years a number of other important papers have further defined the important role HDL-cholesterol plays in the pathobiology of atherosclerosis. These studies have focused on three general areas: HDL-cholesterol metabolism and the reverse cholesterol transport pathway; novel therapeutic interventions and their effects on coronary artery disease as assessed through non-invasive imaging modalities; and finally a re-analysis of previous outcomes trials with established HDL-cholesterol modifying agents. SUMMARY: The results of the Armed Forces Regression Study fit nicely within the evolving paradigm of targeting HDL-cholesterol in patients at risk of cardiovascular events. The use of niacin and well-tolerated fibrates as an adjunct to statins or as primary therapy in patients intolerant of statins appears reasonable in patients with low levels of HDL-cholesterol and at high risk of cardiovascular events. The further development of novel therapeutic approaches, in addition to broadening our pharmacological armamentarium, should further advance our understanding of HDL-cholesterol.

Hypertriglyceridemia-why, when and how should it be treated?⁶¹

The relationship between serum triglyceride levels and cardiovascular disease has remained enigmatic despite four decades of research. The majority of the available evidence tends to support the role of hypertriglyceridemia as an independent risk factor for cardiovascular disease. However, there are no guidelines recommending a target triglyceride level for prevention of cardiovascular disease. The focus of lipid lowering therapy still remains the reduction of global cardiovascular risk by optimizing LDL cholesterol levels. Therapeutic options for triglyceride-lowering include lifestyle modification and pharmacological agents, such as fibrates, omega 3 fatty acids and niacin. Post-hoc analyses of the Helsinki Heart Study, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial and Bezafibrate Infarction Prevention Study suggest a beneficial effect of the treatment of hypertriglyceridemia with fibrates, mainly in obese subjects with insulin resistance. However, in order to establish the actual clinical relevance of lowering triglyceride levels, prospective trials need to be conducted with the specific purpose of studying the effects of triglyceride reduction on clinical end points, i.

e. coronary events and stroke.

Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial⁶².

BACKGROUND: Patients with type 2 diabetes mellitus are at increased risk of cardiovascular disease, partly owing to dyslipidaemia, which can be amenable to fibrate therapy. We designed the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study to assess the effect of fenofibrate on cardiovascular disease events in these patients. METHODS: We did a multinational, randomised controlled trial with 9795 participants aged 50-75 years, with type 2 diabetes mellitus, and not taking statin therapy at study entry. After a placebo and a fenofibrate run-in phase, we randomly assigned patients (2131 with previous cardiovascular disease and 7664 without) with a total-cholesterol concentration of 3.0-6.5 mmol/L and a total-cholesterol/HDL-cholesterol ratio of 4.0 or more or plasma triglyceride of 1.0-5.0 mmol/L to micronised fenofibrate 200 mg daily (n=4895) or matching placebo (n=4900). Our primary outcome was coronary events (coronary heart disease death or non-fatal myocardial infarction); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularisation). Analysis was by intention to treat. The study was prospectively registered (number ISRCTN 64783481). FINDINGS: Vital status was confirmed on all but 22 patients. Averaged over the 5 years' study duration, similar proportions in each group discontinued study medication (10% placebo vs 11% fenofibrate) and more patients allocated placebo (17%) than fenofibrate (8%; p<0.0001) commenced other lipid treatments, predominantly statins. 5.9% (n=288) of patients on placebo and 5.2% (n=256) of those on fenofibrate had a coronary event (relative reduction of 11%; hazard ratio [HR] 0.89, 95% CI 0.75-1.05; p=0.16). This finding corresponds to a significant 24% reduction in non-fatal myocardial infarction (0.76, 0.62-0.94; p=0.010) and a non-significant increase in coronary heart disease mortality (1.19, 0.90-1.57; p=0.22). Total cardiovascular disease events were significantly reduced from 13.9% to 12.5% (0.89, 0.80-0.99; p=0.035). This finding included a 21% reduction in coronary revascularisation (0.79, 0.68-0.93; p=0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (p=0.18). Fenofibrate was associated with less albuminuria progression (p=0.002), and less retinopathy needing laser treatment (5.2%vs 3.6%, p=0.0003). There was a slight increase in pancreatitis (0.5%vs 0.8%, p=0.031) and pulmonary embolism (0.7%vs 1.1%, p=0.022), but no other significant adverse effects. INTERPRETATION: Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations. The higher rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit.

The role of fibrates in managing hyperlipidemia: mechanisms of action and clinical efficacy⁶³.

At a time when the lipid management guidelines give more and more emphasis to the identification and treatment of high-risk patients with the metabolic syndrome and diabetes, there is an obvious need to balance the known effects of low-density lipoprotein (LDL) lowering with the new evidence of clinical efficacy derived from the adjustment of high-density lipoprotein (HDL) and triglyceride levels. Whereas the statins remain the drug of choice for patients who need to reach the LDL goal, fibrate therapy may represent the best intervention for subjects with atherogenic dyslipidemia and an LDL already close to goal. In addition, the concomitant use of fibrates may significantly reduce cardiovascular risk in patients whose LDL is controlled by statin therapy. In this review, we evaluate the pharmacologic properties of the fibrate drugs, with particular attention to the effects of peroxisome proliferator activated receptor activation in the control of dyslipidemia as well as in the attenuation of arterial inflammation. Clinical trials of fibrates, such as the Helsinki Heart Study, Veterans Affairs High-density lipoprotein Intervention Trial, Diabetes Atherosclerosis Intervention Study, and Bezafibrate Infarction Prevention trial, have conjured up a scenario for the clinical utility of fibrates and their possible superiority to statins in the management of obese, insulin-resistant, and diabetic patients presenting with near-goal LDL and inappropriate HDL and triglyceride levels.

Relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease⁶⁴.

BACKGROUND: It remains unclear whether hypertriglyceridemia is an independent risk factor for coronary heart disease (CHD), and whether fasting and nonfasting triglyceride (TG) levels are equally predictive. METHODS: A total of 2809 (of 12 866) men randomized during 1973 through 1975 into the Multiple Risk Factor Intervention Trial with fasting and nonfasting TG levels measured at baseline were followed up for CHD incidence and death. Proportional hazards regression models were used to assess associations of fasting and nonfasting TG levels with CHD. RESULTS: Average fasting and nonfasting TG levels were 187 and 284 mg/dL (2.11 and 3.21 mmol/L), respectively. Prevalence of hypertriglyceridemia (200 mg/dL [2.26 mmol/L] or more) was 31% for fasting and 61% for nonfasting. There were 175 nonfatal or fatal CHD events during 8 years and 328 CHD deaths during 25 years. Compared with TG levels less than 200 mg/dL, risk factor-adjusted hazard ratios for CHD mortality for hypertriglyceridemia were 1.24 (P =.09) for fasting and 1.26 (P =.07) for nonfasting. For nonfatal or fatal CHD, fasting and nonfasting TG levels were similarly predictive with hazard ratios of 1.64 (P =.004) for fasting and 1.46 (P =.03) for nonfasting. These associations for fasting TG levels were assessed to be underestimated by 56% because of regression dilution bias, with attenuation likely greater for nonfasting TG levels. CONCLUSIONS: Greater ease of obtaining nonfasting than fasting measurements, greater prevalence of hypertriglyceridemia with nonfasting than fasting

values, and similarly increased risk with each indicate that nonfasting TG levels may be more useful than fasting ones for risk stratification.

Hypertriglyceridemia: associated risks and effect of drug treatment⁶⁵.

Accumulating evidence indicates that hypertriglyceridemia (HTG) is a risk factor for cardiovascular disease. This increased risk is probably substantially mediated through the metabolic interrelationships between serum triglyceride (TG) levels and other risk factors, such as the atherogenic lipid profile (low high density lipoprotein-cholesterol levels and elevated small dense low density lipoprotein levels), insulin resistance, a prothrombotic propensity and low grade systemic inflammation. TG-lowering strategy in patients with HTG encompasses dietary modification and pharmacological agents, such as fibric acid derivatives, fish-oil and hydroxymethylglutaryl coenzyme A reductase inhibitors, which have, besides their known effects on the atherogenic lipid profile, beneficial effects on other determinants of cardiovascular disease. However, in spite of data from trials investigating fibric acid derivative-induced reduction in coronary events in patients with distinct types of hyperlipidemia, no specific trials have been performed that investigated this risk reduction in patients with HTG, in whom other cardiovascular risk factors are clustered as well. Small-scale studies on determinants of cardiovascular disease in patients with HTG and post-hoc analyses of the Helsinki Heart, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial and Bezafibrate Infarction Prevention trials in patients with high serum TG levels suggest a drug-induced reduction in cardiovascular events. However, a specific trial should be conducted to investigate the effects of lipid-lowering therapy on clinical end-points in patients with HTG of defined types.

Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study⁶⁶.

BACKGROUND: Atherosclerosis is the most common complication of diabetes. Correction of hyperglycaemia helps to prevent microvascular complications but has little effect on macrovascular disease. Post-hoc analyses of diabetic subpopulations in lipid intervention trials suggest that correction of lipoprotein abnormalities will lead to a decrease in coronary-artery disease. The Diabetes Atherosclerosis Intervention Study (DAIS) was specifically designed to assess the effects of correcting lipoprotein abnormalities on coronary atherosclerosis in type 2 diabetes. **METHODS:** 731 men and women with type 2 diabetes were screened by metabolic and angiographic criteria. 418 were randomly assigned micronised fenofibrate (200 mg/day) or placebo for at least 3 years. They were in good glycaemic control (mean haemoglobin A1c 7.5%), had mild lipoprotein abnormalities, typical of type 2 diabetes, and at least one visible coronary lesion. Half had no previous clinical coronary disease. Initial and final angiograms followed a standard protocol and were analysed by a computer-assisted quantitative approach. Missing data for the primary endpoints (minimum lumen diameter, mean segment diameter, and mean percentage stenosis) were imputed. Analyses were by intention to treat. **FINDINGS:** Total plasma cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride concentrations all changed significantly more from baseline in the fenofibrate group (n=207) than in the placebo group (n=211). The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean 2.11 [SE 0.594] vs 3.65 [0.608]%, p=0.02), a significantly smaller decrease in minimum lumen diameter (-0.06 [0.016] vs -0.10 [0.016] mm, p=0.029), and a non-significantly smaller decrease in mean segment diameter (-0.06 [0.017] vs -0.08 [0.018] mm, p=0.171). The trial was not powered to examine clinical endpoints, but there were fewer in the fenofibrate group than the placebo group (38 vs 50). **INTERPRETATION:** DAIS suggests that treatment with fenofibrate reduces the angiographic progression of coronary-artery disease in type 2 diabetes. This effect is related, at least partly, to the correction of lipoprotein abnormalities, even those previously judged not to need treatment.

[Fibrates in the secondary prevention of ischemic cardiopathy]⁶⁷

Clinical trials have demonstrated that reduction of low density lipoprotein cholesterol (LDL-C) reduces the incidence of major cardiac events in patients with coronary heart disease (CHD). Recently, two major secondary prevention trials that evaluated the impact of increasing low serum levels of high density lipoprotein cholesterol (HDL-C) and decreasing serum triglycerides on cardiovascular morbidity and mortality were published. This paper briefly summarizes the characteristics and results of these two studies. In the veterans Affairs HDL Intervention Study (VA-HIT), LDL-C was not changed; HDL-C increased 6.0% and triglycerides were reduced 31% by gemfibrozil. The lipid changes in the Bezafibrate Infarction Prevention (BIP) study were LDL-C -6.5%, HDL-C 18%; and triglycerides -21%. In VA-HIT, there was a 22% reduction (p = 0.006) in major CHD events, whereas in the BIP study a nonsignificant reduction of only 9.4% was observed. It is not clear why the effectiveness of fibrate therapy was different in the two studies. From these results it has been suggested that for most CHD patients, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) will remain the initial drugs of choice, but fibrates may be of use in a subgroup of patients.

Differentiating the effects of raising low levels of high-density lipoprotein cholesterol versus lowering normal triglycerides: further insights from the Veterans Affairs High-Density Lipoprotein Intervention Trial⁶⁸.

In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), a 6% increase in high-density lipoprotein cholesterol (HDL-C) was associated with a 22% reduction in the incidence of fatal and nonfatal myocardial infarction and death from coronary artery disease. A curvilinear correlation was demonstrated between incremental changes in HDL-C and outcome. However, triglyceride levels, which decreased by 31%, were not predictive of clinical events. Some design limitations may be implicated in this lack of statistical correlation between triglycerides and outcome. Evidence from other studies, notably the Framingham Heart Study, the Prospective Cardiovascular Munster Heart Study (PROCAM), and the Baltimore Coronary Observational Long-Term Study (COLTS) suggest that the triglyceride cutpoint of 200 mg/dL is too high. The Bezafibrate Infarction Prevention (BIP) trial found a significant correlation between reduction in death from coronary artery disease and nonfatal MI and reduced triglycerides in a subset of patients with baseline triglycerides >200 mg/dL.

Triglycerides and coronary heart disease: implications of recent clinical trials⁶⁹.

This paper reviews the clinical trial data that offer insight into the question of whether, and in what groups of people, triglycerides might be an appropriate therapeutic target for the primary or secondary prevention of atherosclerotic cardiovascular disease. Two angiographic trials (the Lopid Coronary Angiography Trial and the Bezafibrate Coronary Atherosclerosis Intervention Trial) and three clinical endpoint trials (the Helsinki Heart Study, the Bezafibrate Infarction Prevention Study, and the VA HDL Intervention Trial) are reviewed. Hypertriglyceridemia per se is probably not an appropriate therapeutic target for the prevention of atherosclerotic cardiovascular disease because it is a poor marker of atherogenic risk and because there have been no clinical trials that have directly addressed the question of whether lowering the triglyceride level reduces the number of clinical events. The studies reviewed here, however, suggest that patients with established coronary heart disease and a high triglyceride level, in association with either a low high-density lipoprotein-cholesterol level or perhaps other features of the metabolic syndrome, such as obesity, diabetes, or hypertension, may benefit from fibrate therapy. For patients without established coronary heart disease, it is reasonable to consider hypertriglyceridemia as a risk marker prompting the aggressive treatment of other risk factors such as hypertension, diabetes, high low-density lipoprotein-cholesterol, and obesity.

Evidence that triglycerides are an independent coronary heart disease risk factor⁷⁰.

In the past, the relation between hypertriglyceridemia and coronary heart disease (CHD) has been uncertain. However, a recent multivariate analysis of 8-year follow-up data from the large-scale Prospective Cardiovascular Münster study found hypertriglyceridemia to be an independent risk factor for major coronary events after controlling for low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. Hypertriglyceridemia combined with elevated LDL cholesterol and high LDL:HDL cholesterol ratio (>5) increased the CHD event risk by approximately sixfold. Similarly, a large meta-analysis of 17 prospective trials reported hypertriglyceridemia to be an independent risk factor for cardiovascular disease. In this study, an 88 mg/dl (1.0 mmol/L) increase in plasma triglyceride levels significantly increased the relative risk of cardiovascular disease by approximately 30% in men and 75% in women; the corresponding rates were somewhat lower (14% and 37%) but still statistically significant after adjustment for HDL cholesterol level. These data and observations from patients in the Helsinki Heart Study and the Stockholm Ischemic Heart study, that the greatest coronary benefit during lipid-lowering drug therapy occurred among hypertriglyceridemic patients, argue strongly for an independent role for hypertriglyceridemia in CHD risk. In the recent Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial, the use of gemfibrozil to raise HDL cholesterol levels and lower levels of triglycerides without lowering LDL cholesterol levels reduced coronary events in men with established CHD, whereas preliminary results from the Bezafibrate Infarction Prevention Trial indicate a reduction in coronary end points in patients with elevated baseline triglyceride levels. To achieve the greatest possible reduction in CHD risk, antihyperlipidemic treatment strategies should also be aimed at reducing elevated triglycerides.

Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group⁷¹.

BACKGROUND: Although it is generally accepted that lowering elevated serum levels of low-density lipoprotein (LDL) cholesterol in patients with coronary heart disease is beneficial, there are few data to guide decisions about therapy for patients whose primary lipid abnormality is a low level of high-density lipoprotein (HDL) cholesterol. **METHODS:** We conducted a double-blind trial comparing gemfibrozil (1200 mg per day) with placebo in 2531 men with coronary heart disease, an HDL cholesterol level of 40 mg per deciliter (1.0 mmol per liter) or less, and an LDL cholesterol level of 140 mg per deciliter (3.6 mmol per liter) or less. The primary study outcome was nonfatal myocardial infarction or death from coronary causes. **RESULTS:** The median follow-up was 5.1 years. At one year, the mean HDL cholesterol level was 6 percent higher, the mean triglyceride level was 31 percent lower, and the mean total cholesterol level was 4 percent lower in the gemfibrozil group than in the placebo group. LDL cholesterol levels did not differ significantly between the groups. A primary event occurred in 275 of the 1267 patients assigned to placebo (21.7 percent) and in 219 of the 1264 patients assigned to gemfibrozil (17.3 percent). The overall reduction in the risk of an event was 4.4 percentage points, and the reduction in relative risk was 22 percent (95 percent confidence interval, 7 to 35 percent; P=0.006). We observed a 24

percent reduction in the combined outcome of death from coronary heart disease, nonfatal myocardial infarction, and stroke ($P < 0.001$). There were no significant differences in the rates of coronary revascularization, hospitalization for unstable angina, death from any cause, and cancer. **CONCLUSIONS:** Gemfibrozil therapy resulted in a significant reduction in the risk of major cardiovascular events in patients with coronary disease whose primary lipid abnormality was a low HDL cholesterol level. The findings suggest that the rate of coronary events is reduced by raising HDL cholesterol levels and lowering levels of triglycerides without lowering LDL cholesterol levels.

Recent developments in the treatment of hypertriglyceridemia⁷².

Hypertriglyceridemia is now recognized as an independent risk factor of coronary artery disease (CAD). A recent secondary prevention study of CAD with a statin suggested that it may be prudent to target fasting triglycerides to less than 150 mg/dL. Secondary prevention trials of CAD with drugs acting primarily on triglycerides (fibrates) have shown that reducing triglycerides and increasing high-density lipoprotein (HDL) cholesterol, without significantly affecting low-density lipoprotein cholesterol slows down coronary artery luminal narrowing (Lopid Coronary Angiography Trial [LOCAT], Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT], Bezafibrate Infarction Prevention [BIP]). Furthermore, Veterans Administration-HDL Intervention Trial (VA-HIT) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 (GISSI) studies recently showed that gemfibrozil and fish oils, respectively, decreased CAD mortality in secondary prevention trials. Statins are also capable of significantly reducing high triglyceride levels. Further clinical studies are necessary to confirm in terms of mortality the beneficial effect of reducing triglycerides and increasing high-density lipoprotein cholesterol in secondary CAD prevention; whereas, in primary prevention the beneficial effect of drastically reducing triglycerides by the way of pharmacology needs to be proved.

Safety and efficacy of Omacor in severe hypertriglyceridemia⁷³.

BACKGROUND: Severe hypertriglyceridemia is a risk factor for acute pancreatitis, therefore decreasing serum triglyceride concentrations is an important component of risk management. Omega-3 fatty acids are well known hypotriglyceridemic agents, but their efficacy in severe forms of the disorder is not well documented. Our objective was to examine the effects of Omacor, a drug composed of 85% omega-3 fatty acid ethyl esters. **METHODS:** Forty-two patients with triglyceride concentrations between 5.65 and 22.60 mmol/l (500 and 2000 mg/dl) were studied in a prospective, double-blind, placebo-controlled trial of Omacor (4 g/day for 4 months). **RESULTS:** Compared with baseline values, Omacor significantly reduced mean triglyceride concentrations by 45% ($P < 0.00001$), cholesterol by 15% ($P < 0.001$), very-low-density lipoprotein cholesterol by 32% ($P < 0.0001$) and cholesterol:high density lipoprotein (HDL) cholesterol ratio by 20% ($P = 0.0013$), and increased HDL cholesterol by 13% ($P = 0.014$) and low-density lipoprotein cholesterol by 31% ($P = 0.0014$). The placebo had no effect on these parameters. Omacor was well tolerated and no patient discontinued medication because of side effects. **CONCLUSIONS:** Four capsules of Omacor per day markedly decreased triglyceride concentrations in patients with severe hypertriglyceridemia. The availability of a potent and safe omega-3 fatty acid preparation for this patient population should diminish the risk for acute pancreatitis, and may also reduce the long-term risk for cardiovascular disease.

Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT])⁷⁴.

Recent reports indicate that most coronary events originate from plaques causing $< 50\%$ diameter stenosis. A subgroup analysis of the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) data was undertaken to determine the effects of bezafibrate in relation to baseline narrowing. BECAIT included 92 male postacute myocardial infarction patients < 45 years of age. Each received double-blind treatment with bezafibrate (200 mg 3 times daily) or placebo for 5 years, together with a low-fat diet. Coronary angiography was performed at baseline and after 2 and 5 years. The mean minimum lumen diameter of lesions causing 20% to $< 50\%$ diameter stenosis at baseline did not narrow over 5 years in the bezafibrate group and decreased by 0.15 mm in the placebo group ($p < 0.05$). In segments with $>$ or $= 50\%$ diameter stenosis at baseline, no change was seen in either of the 2 groups. In the analysis including only segments with 20% to $< 50\%$ stenosis at baseline, coronary events were seen in 7 of 40 patients with a progression in minimum lumen diameter of more than the median value and in 3 of 41 patients with a change less than the median value. Thus, bezafibrate had a preferential effect in slowing the progression of narrowings causing $< 50\%$ stenosis at baseline in young men followed up for a 5-year period after acute myocardial infarction.

Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Lopid Coronary Angiography Trial (LOCAT) Study Group⁷⁵.

BACKGROUND: Studies have shown that treatment of hyperlipidemia, especially lowering of plasma LDL levels, retards the progression of coronary atherosclerosis and prevents clinical cardiovascular events. No such studies have focused on subjects with low levels of HDL cholesterol. **METHODS AND RESULTS:** We randomly assigned 395 post-coronary bypass

men, who had an HDL cholesterol concentration ≤ 1.1 mmol/L and LDL cholesterol ≤ 4.5 mmol/L, to receive gemfibrozil 1200 mg/d or placebo. Coronary angiography was performed at baseline and after, on average, 32 months of therapy. Changes in coronary dimensions were assessed by computer-assisted analysis. Average on-trial serum triglyceride concentrations were 1.69 ± 0.68 and 1.02 ± 0.37 , total cholesterol 5.48 ± 0.68 and 4.83 ± 0.63 , LDL cholesterol 3.84 ± 0.59 and 3.39 ± 0.56 , and HDL cholesterol 0.88 ± 0.15 and 0.98 ± 0.17 mmol/L in the placebo and gemfibrozil groups, respectively (mean \pm SD, each $P < .001$). The change in per-patient means of average diameters of native coronary segments was -0.04 ± 0.11 mm in the placebo group and -0.01 ± 0.10 mm in the gemfibrozil group ($P = .009$). The equivalent changes in minimum luminal diameters of stenoses were -0.09 ± 0.18 and -0.04 ± 0.15 mm, respectively ($P = .002$). A similar, albeit nonsignificant, trend toward treatment benefit was found in the predefined primary study end point, segments unaffected by grafts and those distal to graft insertions. In aortocoronary bypass grafts, 23 subjects (14%) assigned to placebo had new lesions in the follow-up angiogram, compared with 4 subjects (2%) assigned to gemfibrozil ($P < .001$). **CONCLUSIONS:** Gemfibrozil therapy retarded the progression of coronary atherosclerosis and the formation of bypass-graft lesions after coronary bypass surgery in men with low HDL cholesterol as their main lipid abnormality.

Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment⁷⁶

BACKGROUND. We studied the joint effect of baseline triglyceride and lipoprotein cholesterol levels on the incidence of cardiac end points in the trial group ($n = 4,081$) of the Helsinki Heart Study, a 5-year randomized coronary primary prevention trial among dyslipidemic middle-aged men. The relative risks (RR) were calculated using Cox proportional hazards models with a dummy variable technique that allows simultaneous study of subgroup combinations from the placebo and treatment groups. **METHODS AND RESULTS.** In the placebo group ($n = 2,045$), the low density lipoprotein cholesterol (LDL-C)/high density lipoprotein cholesterol (HDL-C) ratio was the best single predictor of cardiac events. This ratio in combination with the serum triglyceride level revealed a high-risk subgroup: subjects with LDL-C/HDL-C ratio greater than 5 and triglycerides greater than 2.3 mmol/l had a RR of 3.8 (95% CI, 2.2-6.6) compared with those with LDL-C/HDL-C ratio less than or equal to 5 and triglyceride concentration less than or equal to 2.3 mmol/l. In subjects with triglyceride concentration greater than 2.3 mmol/l and LDL-C/HDL-C ratio less than or equal to 5, RR was close to unity (1.1), whereas in those with triglyceride level less than or equal to 2.3 mmol/l and LDL-C/HDL-C ratio greater than 5, RR was 1.2. The high-risk group with LDL-C/HDL-C ratio greater than 5 and triglyceride level greater than 2.3 mmol/l profited most from treatment with gemfibrozil, with a 71% lower incidence of coronary heart disease events than the corresponding placebo subgroup. In all other subgroups, the reduction in CHD incidence was substantially smaller. **CONCLUSIONS.** Serum triglyceride concentration has prognostic value, both for assessing coronary heart disease risk and in predicting the effect of gemfibrozil treatment, especially when used in combination with HDL-C and LDL-C.

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